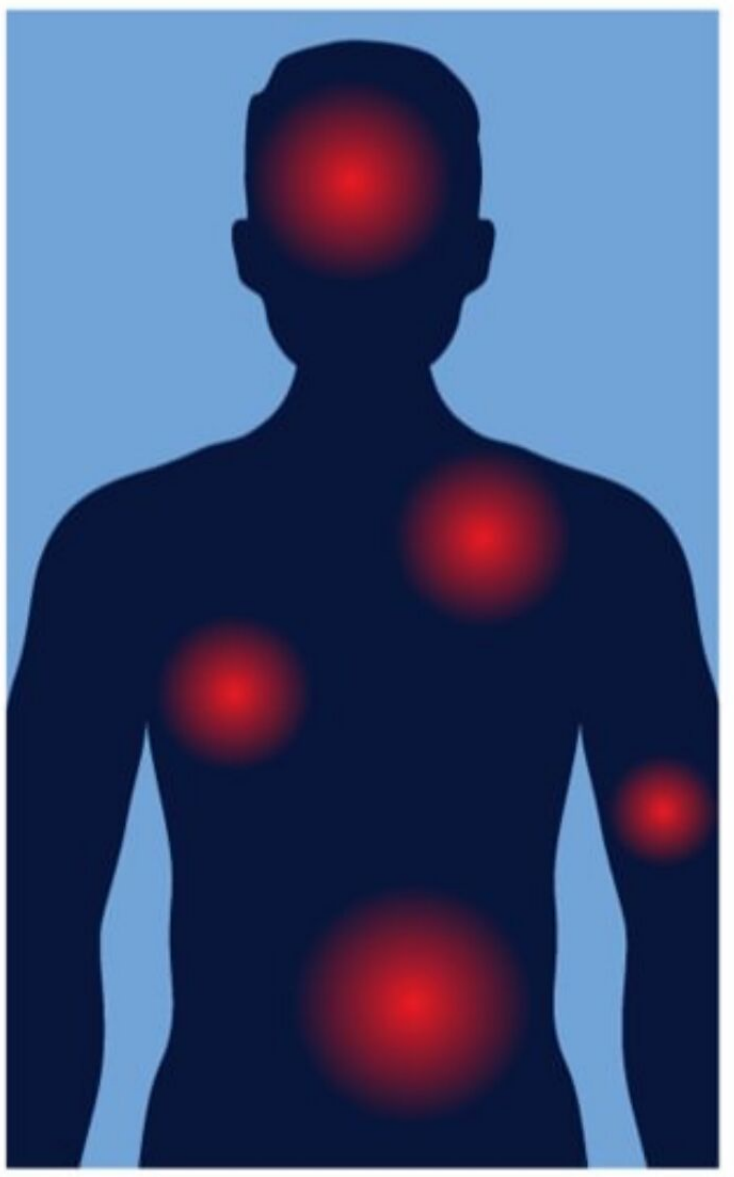
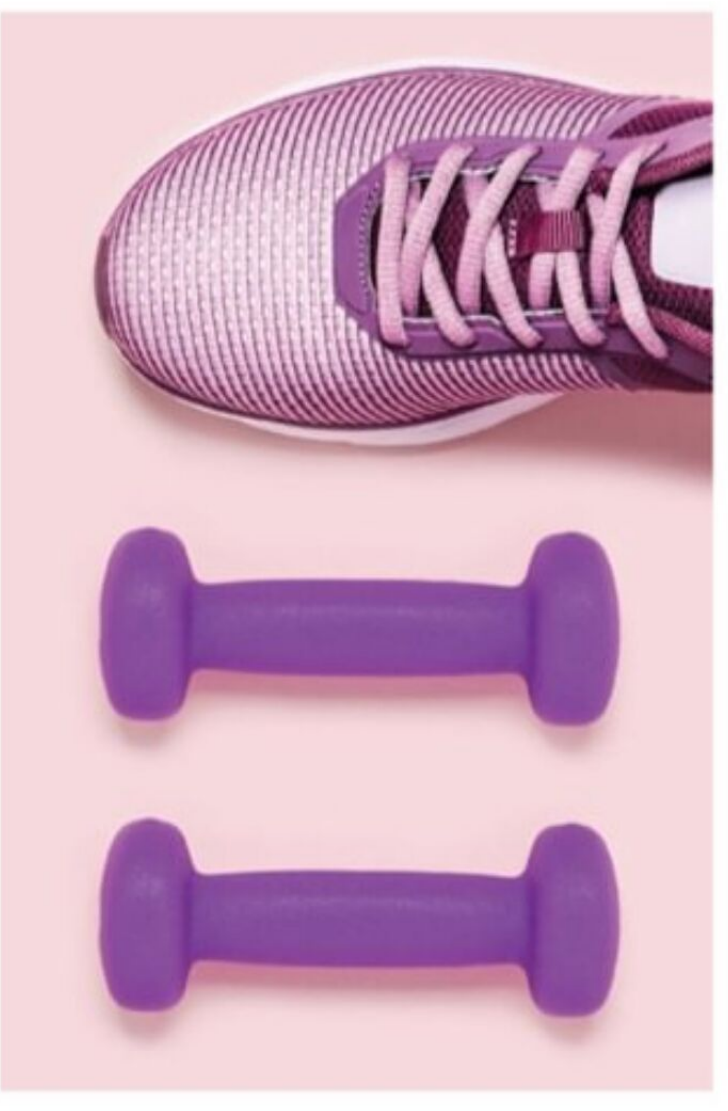
SPECIAL TIME EDITION

Anti-Inflammation

The Science, the Research, the Healing

Foods That Soothe • What the Science Says • The Best Exercises





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This edition is for general information purposes only, and nothing contained in it is intended to be a substitute for the individualized advice of a physician or other health professional. The reader should consult the appropriate health professional in matters relating to physical and mental health and particularly with respect to any symptoms that may require diagnosis or treatment.

UNDERSTANDING INFLAMMATION

The body's immune response can protect and heal us, but it can also wreak havoc over time. Balance comes with an active, healthy lifestyle.

BY MARKHAM HEID

IN SOME WAYS, INFLAMMATION IS STRAIGHTforward and easy to understand. It is the immune system's primary response to injury, illness, or infection. Inflammation protects and heals us. Without it, none of us would last long.

On the other hand, the underlying causes and consequences of inflammation are endlessly complex. Take two people and expose them to the exact same threat—a bee sting, for example—and their immune system's inflammatory response may be dramatically different. While one person might develop a small, hardly noticeable red bump, the other could experience life-threatening anaphylaxis.

"Inflammation is the body's natural response to fighting something bad," says Jason Hou, MD, a gastroenterologist and associate professor of medicine at Baylor College of Medicine and the Michael E. DeBakey VA Medical Center in Houston. "Our body uses inflammation to our benefit to destroy viruses or bacteria, or even cancer cells." But those helpful processes are only half of the inflammation story. "If uncontrolled or turned on when it's not supposed to be, inflammation can be a very harmful thing that can cause a lot of problems," Hou says.

Physicians and other medical experts have been trying to untangle the intricacies of inflammation for thousands of years. Millennia-old papyri from ancient Egypt offer the first written record of inflammation. And more than 2,000 years ago, the Roman encyclopedist Cornelius Celsus identified four of the major symptoms of inflammation: redness, swelling, pain, and fever.

But while we've known about inflammation since the dawn of recorded history, our recognition that it may be a driving force in the development of cancer and other chronic diseases is a very recent insight. Likewise, the relationship between the body's stress responses and inflammation—and the way living with chronic low levels of inflammation may put a person at risk for illnesses of both the mind and body—is something medical scientists have only lately begun to fully appreciate.

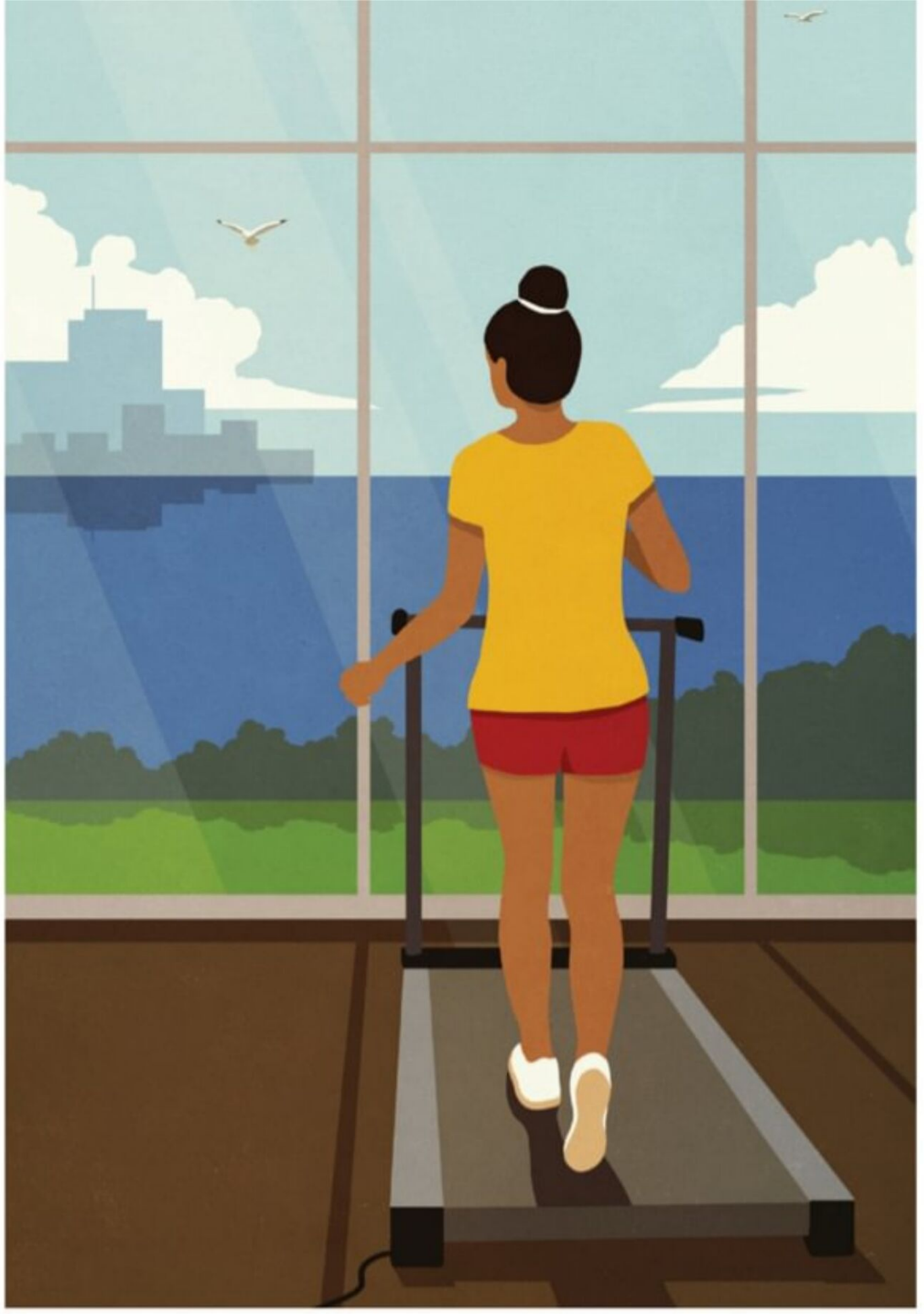
Experts are still refining their understanding of inflammation and its precise roles in health and illness, work that is likely to continue for many years to come. But it's clear that managing inflammation on a day-to-day basis can play a crucial role in maintaining whole-body health. Things like diet, exer-

cise, sleep, and stress management all appear to be important pieces of the inflammation-health puzzle.

Inflammation Under the Skin

The inflammatory process begins when the immune system detects a threat. That threat may be real and already present—such as a flu virus—but it might also be imagined or anticipated. (More on that in a minute.) A whole host of immune cells are, together, responsible for this threat detection. Some circulate in the blood, while others reside in the body's tissues. These immune cells include neutrophils, macrophages, and lymphocytes, to name just a few.

When these immune cells perceive something to be threatening, they trigger the release of a group of pro-inflammatory proteins called cytokines. There are numerous cytokines, and each of them contributes to the body's inflammatory process in specific ways. It's the action of cytokines that produces swelling, heat, and the other detectable symptoms of inflammation, often by summoning more blood to a specific part of the body. But while some cytokines stoke inflammation, others are responsible for mellowing it. "Some cytokines turn inflammation up, while others turn it down," Hou explains.



While a single workout session triggers a localized inflammatory response, frequent exercise can help keep chronic inflammation in check.

The inflammatory process can range from mild to severe. Returning to the bee sting example, both the person who develops a small red bump and the person who develops anaphylaxis are experiencing inflammation. However, one person's inflammatory response is far, far more aggressive and widespread than the other's. In this example, a little inflammation is appropriate; the bee sting is a minor injury that could introduce a pathogen into the body, so it's a good thing that the immune system responds to the threat with localized inflammation. Without that response, the sting is more likely to become infected, which could create a far greater threat.

On the other hand, major swelling and anaphylaxis is an outsize and dangerous response to a relatively minor wound.

That said, even mild or "low-grade" inflammation can be a problem if it arises too often or persists for too long. That's what tends to happen when someone experiences chronic stress, and this helps explain how everyday inflammation can contribute to the development of a host of major illnesses and diseases.

Stress and Inflammation

Just as inflammation is sometimes described as either "good" or "bad," people often talk about stress

in these same terms. Brief bouts of stress are often regarded as good or even healthy, while persistent stress is deemed bad. This is a little misleading: Whether stress is helpful or harmful depends a lot on the situation. However, in simple terms, short, or "acute," periods of stress that last a few hours or a few days are usually considered normal and healthy.

"When we talk about acute stress, we're often thinking about short-term stressors that are relatively constrained and over with quickly, like a bad day at work or an argument with a spouse," says Darlene Kertes, PhD, a stress researcher and associate professor of behavioral and cognitive neuroscience at the University of Florida. It's the longer, all-the-time periods of "chronic" stress that get people into trouble, she says, and inflammation plays a key role in the harm associated with long-lasting stress.

All types of stress—long or short, heavy or mild—activate the body's sympathetic nervous system (a.k.a. the "fight-or-flight" system). "The fight-or-flight response mobilizes our body to meet whatever challenge we're dealing with," Kertes says. While that response evolved over millions of years to help humans and their forebears deal with life-or-death threats, the same system switches on when we experience interpersonal conflicts, work deadlines, and other modern-day stressors. (Our lives and our world may have evolved, but our body's methods of meeting life's challenges are the same.)

During this fight-or-flight response, the body prepares for physical action: Heart rate increases, digestion slows, and breathing speeds up. The airway muscles relax to allow for the better absorption of oxygen. Meanwhile, brain activity also shifts in response to stress. Research has found that aspects of memory storage and retrieval weaken while emotionality increases and decision-making—for better or worse—speeds up. Just as stress and its associated sympathetic activity get the brain and body ready for a challenge, stress also causes the immune system to make preparations. Blood levels of inflammation-stoking white blood cells (particularly neutrophils) increase, and the activity of pro-inflammatory cytokines also ramps up. The immune system is shifting into a state of high alert and simmering, low-level inflammation that will allow it to quickly address any injuries or other assaults.

Again, none of this is a problem if the stress is short-lived. However, when someone is chronically stressed, the immune system can become dysregulated. Short-acting neutrophils are displaced by macrophages and other white blood cells that promote higher levels of inflammation. Meanwhile, levels of the hormone cortisol rise.

While cortisol is often thought of as "the stress hormone," its job is actually to calm the surge in inflammation that accompanies stress, Kertes says. (The synthetic corticosteroids used to treat many inflammatory conditions are, as their name suggests, very similar to the cortisol the body produces itself to manage inflammation.) During brief periods of acute stress, cortisol floods the blood and calms down all those inflammation-stoking immune cells and proteins. But if stress is chronic and cortisol levels remain elevated for long periods of time, the body's immune cells and related systems can become "desensitized" to cortisol's effects, Kertes explains. This desensitization can cause inflammation to rage out of control. It also interferes with cortisol's typical "repair and maintenance" work, she says.

LOW-GRADE INFLAMMATION CAN BE A PROBLEM IF IT ARISES TOO OFTEN OR PERSISTS FOR TOO LONG.

As this desensitization to cortisol occurs, a person may at the same time become more sensitized to psychological stress. "If you're continually exposed to stress, you're teaching the brain that it exists in a toxic, threatening environment and that it needs to be on alert all the time," Kertes says. "So it becomes hyperresponsive." In other words, stress tends to breed more stress.

The Health Consequences

There are many ways that all-the-time inflammation—even mild inflammation—can interfere with a person's health. Sticking first with stress-related inflammation, experts say heart trouble is a concern. "Stress and inflammation can initiate an

increase in blood pressure, which increases the pressure on the walls of the blood vessels and can therefore lead to damage and heart disease," says Amgad Makaryus, MD, a cardiologist and professor at Hofstra University and Northwell Health in East Meadow, New York. "Cardiologists are paying more attention to stress and lifestyle and all these other factors that control inflammation, because we're becoming more aware of the downstream effects of inflammation on cardiovascular disease and lots of other problems."

Gut health is another area of intense research focus. "Stress can affect several aspects of normal gastrointestinal physiology—everything from influencing the secretion of gastric acid and other digestive enzymes to changing motility patterns both in the small and large intestines," says Michael Bailey, PhD, an associate professor of pediatrics and immunity at Ohio State University's Wexner Medical Center who has studied the effects of stress on the gut and immune system.

Bailey says all these stress-induced shifts—mostly via inflammation—can cause short-term stomach pain, constipation, or other gut issues in healthy people, and they can worsen symptoms for those with GI disorders.

Meanwhile, inflammation can lead to fatigue, and headaches (including migraines). It can create pain or make existing pain more intense. In large populations of healthy people, researchers have found that those who have low-grade inflammation tend to feel worse in general, and self-rate their overall physical health lower, than those who do not have low-grade inflammation. There's also evidence that inflammation may contribute to the development and persistence of depression and other psychiatric disorders.

Turning to chronic diseases, almost everything that can go wrong with the brain or body seems to be driven at least in part by too much inflammation. Beginning with cancer, research has found that chronic inflammation may promote the disease "through tissue destruction and scarring, and reshaping of the tissue architecture, as well as contributing to changes in gene expression." Metabolic diseases (such as type 2 diabetes), autoimmune diseases (such as rheumatoid arthritis), and Alzheimer's disease are all closely tied to inflammation.

It is not an exaggeration to say that all illnesses and disease, whether temporary or chronic, are either fueled by or worsened by inflammation. The good news is that we all have some ability to manage inflammation through diet, exercise, and other behaviors.

Controlling Inflammation

While the immune system operates throughout the body, its primary headquarters surround the gut. When you think about it, this makes sense—the most likely way for illness-causing pathogens and other threats to get inside our bodies is via the stuff we consume, so it behooves the immune system to pay extra close attention to the gut and its occupants, including the trillions of bacteria that live there.

As medical researchers have begun to pay closer attention to the gut and its microbial communities, they've gained a greater awareness of how GI inflammation may affect overall health and functioning. "We know that chronic bowel inflammation has an impact on other elements of health and life," says David Rubin, MD, a professor of medicine and co-director of the Digestive Diseases Center at the University of Chicago. "When people are inflamed, even when they don't feel it, we know they may have disrupted sleep patterns." He also mentions the links between bowel inflammation and mental health disorders such as anxiety and depression: "There's evidence that an inflamed bowel may alter neurotransmitters relevant to mood," he says.

The connection between gut inflammation and overall health and functioning has led experts to examine how a person's diet can worsen or tame inflammation. While there's endless discussion online about anti-inflammatory diets—and plenty of people pushing very specific, very restrictive diets to curb inflammation—Rubin says there is no agreed-upon definition of what an anti-inflammatory diet entails, and that any attempts to reduce inflammation via diet are going to involve very broad and commonsense changes.

"We advise patients to eat less processed or ultra-processed foods, and to eat something that resembles a Mediterranean diet that includes a lot of whole foods and green leafy vegetables and olive oil," he says. In line with this advice, a growing body of research has found that ultra-processed foods (which basically means packaged foods made with a lot of additives and preservatives) are associated with low-grade inflamma-

Research suggests that eating foods high in natural antioxidants and polyphenols (protective compounds found in plants) can lower inflammation.

tion and an elevated risk of chronic disease.

Apart from limiting one's intake of ultra-processed foods (yes, easier said than done), physical activity is another healthy way to calm inflammation. "In the general population and populations living with non-communicable disease, there is evidence to suggest that exercise has anti-inflammatory effects," wrote the authors of a 2020 research review on the connection between exercise and inflammation. Exercise not only relieves stress, but it also "blunts" inflammatory pathways, that study found. It's not clear what amount of exercise is optimal for reducing inflammation; this likely varies from person to person. But current public health guidelines, which are supported by ample evidence, recommend that adults aim for 150 to 300 minutes of moderate-intensity physical activity per week (brisk walking, biking, hiking, lifting weights, etc.) or 75 to 150 minutes per week of intense physical activity (such as running or swimming). Ideally the exercise is spread throughout the week, and people should also try to sit less and move around more during the day.

Proper sleep is another pillar of an anti-inflammation lifestyle. "We tend to be more stressed when we don't sleep, and we know poor sleep makes inflammation worse," says Makaryus. While different people have different sleep needs, research generally finds that sleeping between seven and eight hours a night is optimal. Avoiding alcohol, which at any dosage has been found to disrupt aspects of sleep, is also helpful.

Finally, managing stress can be a potent inflammation slayer. A good night's sleep and regular exercise are great ways to reduce stress, but there are others. There is now robust evidence linking mind-body techniques—yoga, breathing exercises, mindfulness meditation, progressive muscle relaxation, tai chi, and other related practices—to the reduction of both stress and inflammation. Many of these practices are now recommended by doctors who treat inflammatory conditions, not as stand-alone therapies but as helpful adjuncts to other forms of treatment.

These kinds of inflammation-busting recommendations (eat whole foods, exercise, reduce stress) may not be surprising. They're pretty intuitive, in fact. And the bulk of the evidence indicates that these are the path that leads to lower inflammation and better overall health.

"Inflammation and stress and sleep and health – all of this is interrelated," Makaryus says. "People think of inflammation as bad, but it's usually just a manifestation of unhealthy choices or illnesses." Inflammation can be the cause of a diverse array of health problems, but it is also a consequence of an unhealthy lifestyle. Each of us has some power to fight it. □

THE FIRES WITHIN

Most of the time, inflammation helps the body fend off various bacteria and parasites. But when inflammation goes awry, it can lead to a host of chronic diseases.

LINKS TO THE MOST SERIOUS DISEASES

A gastroenterologist at Columbia University Medical Center explains how untamed inflammation could be the culprit behind conditions such as heart disease and cancer.

BY SHILPA RAVELLA, MD

IN THE EARLY DAYS OF MY MEDICAL RESIDENCY, I met a man whom I'll call Jason. He arrived in our emergency room on a holiday, nonchalant yet amiable, and complained of mild chest pain. Jason was tall and trim, with a strong South Boston accent and fingertips still faintly stained from his last home-improvement project. He was only 45 years old, and he looked much younger. He didn't smoke, barely drank alcohol, and his cholesterol levels had always been normal. No one in his family had a history of heart disease. He asked us if we could work quickly—he wanted to be home for dinner with his daughters.

We welcomed a likely false alarm. Maybe Jason was having a bout of acid reflux, or even a panic attack. His heart, surely, was as robust as the rest of him. He was young and without any risk factors for heart disease. And he had been in excellent health all of his life. Our minds wandered to other patients and tasks.

But as the day wore on, Jason's symptoms persisted. When the results of his blood tests finally blinked on our pagers, we were shocked to find that he was suffering from a massive heart attack. Jason was rushed to the cardiac catheterization lab, where a cardiologist began threading a thin tube through an artery in his leg in an attempt to open up blockages in the arteries feeding his heart.

As I learned in the ensuing years of training, Jason's story is not unusual. For too many people, the first clue that they have cardiovascular disease is a heart attack or a stroke—or even death. But we wondered, in Jason's case, why it had happened—what was the cause?

Traditionally, doctors address common risk factors for developing cardiovascular disease, including high blood cholesterol levels, diabetes, smoking, and family history. But one of the biggest revelations of 21st-century medicine is the unveiling of another important cause of heart disease, one that may lurk

in the body unseen and unfelt yet increases the risk of someone dropping dead from a heart attack or stroke: inflammation.

Inflammation is a primeval force that evolved with benevolent intent, striving to protect the body against pathogens, poisons, and traumas—all of which ancient humans routinely succumbed to. It can be grasped by the naked eye. Slam your knee on the edge of a table with enough force, for example, and redness, heat, pain, and swelling—the four cardinal signs of inflammation—inevitably ensue as blood flow quickens and vessels dilate, allowing fluid and protein to leak out into tissues. Inflammation works to handle and to eventually heal the wound.

But inflammation is not always helpful, or even harmless. In autoimmune diseases such as rheumatoid arthritis, lupus, and inflammatory bowel disease, it rages against the body's own tissues, disrupting essential functions and ultimately leading to disability. Today, we know that inflammation plays an important role not only in autoimmunity but in many other chronic conditions as well, including heart disease, cancer, obesity, diabetes, and aging. Low-level, invisible inflammation, simmering quietly in the blood of ostensibly healthy people, may be a common thread running through nearly all diseases.

Research reveals that persistent low-level inflammation, which is twice as common as elevated blood cholesterol levels, plays a part in every stage of heart disease, including increasing the risk of plaque rupture, which leads to heart attacks. In fact, half of all heart attacks occur in people with normal cholesterol levels. In 2017, the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) showed that treating low-level inflammation in people who had experienced prior heart attacks—correcting for differences in other factors, such as blood cholesterol, diabetes, and high blood pressure—lowered patients' risk of heart attack, stroke, and even death from cardiac events. In 2020, another large clinical trial found that colchicine, a medication used for centuries by ancient Greeks and Egyptians to treat the glaring, roaring inflammation of gouty arthritis, could also treat the hidden iteration in heart disease, decreasing the risk of cardiac events. Perhaps Jason, seemingly healthy, had been silently inflamed.

Many years after my encounter with Jason, a patient came to my gastroenterology clinic complaining of rectal bleeding. For a couple of years, Rebecca had been noticing small spots of bright blood dotting the toilet paper when she had a bowel movement. This would only happen on occasion, and she insisted hemorrhoids were responsible for the spotting. She was only 34 years old and had no family history of colon cancer. Busy with three kids to care for and chronically short on time, she had put off visiting a gastroenterologist. But when I performed her colonoscopy, I found more than hemorrhoids: a jagged, motley collection of tissue gripped at the walls of her colon, so hard and unforgiving that I couldn't advance my scope through its narrow opening. Imaging scans showed that she had cancer, which had already spread to the liver. It was the first time I had diagnosed colon cancer in someone so young, but it wouldn't be the last. Cancer is invading more collective years of human life than ever before.

While inflammation weaves through the arteries feeding the heart, it may fester in tumors as well. The immune system fights tumors as it does germs, attempting to keep cancerous cells in check. But it

Colchicine comes from the flower colchicum autumnale (opposite). The ancient drug is still used today and can help manage inflammatory conditions such as arthritis.

also betrays the body by helping them to grow and spread. Inflammation fuels cancer in many cases, and cancer—like a cut to the skin—fuels inflammation. Cancer is fed not only by obviously inflamed tissues but by insidious low-level inflammation as well, which doctors typically do not test for. Whether it shows up before or after the birth of a cancer, inflammation can affect all its life stages, from early genetic influences that transform normal cells into malignant ones to the continued growth and spread of cancerous tissue throughout the body. Cancer behaves like a "wound that does not heal," as scientist Harold Dvorak writes. Of course, cancer may arise in non-inflamed tissues as well, and not all types of tissue inflammation carry an equivalent increase in the risk of cancer.

That inflammation is a common element in heart disease and cancer is no coincidence. The intricate link between inflammation and modern chronic diseases is rooted in our evolutionary history. In order to survive infections, famine, and other dangers in brutish ancestral times, we developed a hyperactive immune system and insulin-resistant body adept at storing fat. But our modern environment has been markedly transformed, from the food we eat to the air we breathe, how we move, and more. Our immune system is exceptionally sensitive to the triggers of this new world, portending a higher risk of chronic, hidden inflammation.

Moreover, inflammation is intimately tied to essential life-sustaining processes occurring throughout the body. Metabolic processes, for example, include those that convert food into energy and remove waste. The metabolic syndrome is a group of risk factors associated with heart disease, diabetes, and some cancers: fat around the stomach, high blood pressure, high blood sugar, and unhealthy cholesterol levels. Traditionally, metabolic processes and immune reactions were viewed as distinct entities with disparate functions. But we now know that they are intimately interdependent.

Managing energy and defending the body against infections are both crucial for survival, and they coevolved. Fat cells—which are known to play a part in metabolism—and immune cells derive from the same ancestral cell and share many roles. An excess of fatty tissue, particularly the visceral fat that wraps around abdominal organs, acts like an immune organ, producing a slew of inflammatory molecules. In markedly obese individuals, more than half of the cells making up the fat tissue are actually immune cells. Low-level inflammation may help to explain the ties between obesity and a variety of chronic diseases, including heart disease and cancer.

Chronic diseases are complex entities, and a singular, unifying theory of disease may forever be elusive. But mounting evidence suggests that inflammation is an important common thread running through many distinct diseases. Conditions that tend

to cluster together include not only heart disease, stroke, cancer, diabetes, and obesity but also neurodegenerative conditions like Alzheimer's. If you are diagnosed with any one of these diseases, you are more likely to develop one or more of the others. And it's no accident that these illnesses tend to emerge during the aging process, which itself is tied to inflammation. In fact, "inflammaging"—the hidden inflammation of old age—is one of several essential factors that drive aging in humans.

The idea that inflammation may be a biological mechanism shared by many modern chronic diseases fosters a new understanding of human health. It compels us to approach diagnosing, preventing, and treating these diseases in concert rather than piecemeal fashion. Doing this means delving into the root causes of hidden inflammation, which are largely lifestyle factors, including our diet. The food we eat can promote, prevent—or, in some cases, even treat—inflammation and chronic diseases.

For example, the age-old advice to consume more fiber from whole plant foods takes on new meaning when considered in the context of the immune system and inflammation. One of the most important methods by which fiber exerts its healthful benefits is by manipulating the immune system. A fiber deficiency, present in 95 percent of Americans, is tied to a variety of chronic diseases, including heart disease, cancer, diabetes, obesity, and an overall higher risk of death from these and other diseases.

A sedentary lifestyle is also inflammatory. The consequences of moving too little can manifest not only in obvious ways—excess subcutaneous fat, for example, or chronic disease—but in hidden ones as well. Dozens of human clinical trials across age groups point to the power of regular exercise to calm chronic low-level inflammation. Exercise counters inflammation in many ways. For instance, it shrinks inflammatory visceral fat, which is invisible to the naked eye. And remarkably, even in the absence of weight loss, exercise lowers the numbers of immune cells that infiltrate fat tissue and churn out inflammatory cytokines.

REGULAR EXERCISE CAN SHRINK INFLAMMATORY VISCERAL FAT, WHICH IS INVISIBLE TO THE NAKED EYE.

The ways in which we eat and move are intimately linked to another potential root cause of hidden inflammation: our relationship with the microbes that live inside and around us. The intestinal microbiome, which encompasses trillions of germs—including bacteria, viruses, and fungi—functions like an organ. It has a central role in immune function and inflammation. Fostering critical conversations between our microbes and immune cells means changing not only our diet, which can affect inflammation directly and through the microbiome, but other lifestyle factors as well. When we embrace the natural world, for example, we encounter ancestral microbes that swim in water and soil and air. These microbes evolved alongside humans, and some of them became indispensable to immune health and inflammation.

Today, almost 20 years since my experience with Jason, we know that inflammation is an independent cause of heart disease, and that lifestyle factors play an important part in combating it. We are also attempting to become more adept at catching this silent killer. Blood levels of a molecule known as C-reactive protein (CRP) are elevated in inflamed bodies. In heart disease, a special test called high-sensitivity CRP can be used to detect low-level inflammation that may be present years or even decades before a heart attack or stroke manifests. But existing isolated blood markers tend to be nonspecific: They do not tell us why the inflammation is there or how long it has been around.

New research is focusing on the potential of clusters of markers—inflammatory "signatures"—to better define the state of being silently inflamed. Imaging tests such as magnetic resonance imaging or computed tomography scans may add invaluable information, picking up inflammation that surrounds blood vessels or pointing to inflammatory findings in atherosclerotic plaques that predict rupture.

In the 21st century, as hidden inflammation weaves through our deadliest diseases, unveiling this force—seeing what has long been unseen—is poised to make its mark on medicine. □

THE GUM DISEASE RISK

Why inflammation in your mouth may raise your risk of cancer.

BY AMANDA MACMILLAN

Women with gum disease are 14 percent more likely to develop cancer than those with healthy teeth and gums, according to a study published in *Cancer Epidemiology, Biomarkers & Prevention.* The link appears to be strongest for esophageal cancer, but associations were also found between poor oral health and lung, gallbladder, breast, and skin cancer.

The study looked at data from nearly 66,000 postmenopausal women, ages 54 to 86, who were followed for about eight years. At the start of the study, they completed a health survey and reported whether they had ever been diagnosed with periodontal disease, an inflammation of the gums that can lead to tooth loss.

Gum disease is caused by sticky, bacteria-laden plaque that forms on teeth. In the early stages, known as gingivitis, the gums can be swollen and bleed easily. Daily flossing and brushing can usually reverse gingivitis. If plaque is left on teeth, it can progress to periodontal disease, which is inflammation around the teeth that causes gums to pull away and form pockets, which can trap more food and bacteria. With time, the bacteria, inflammation, and the body's immune reaction can damage teeth and supporting bone structures, which can lead to tooth loss.

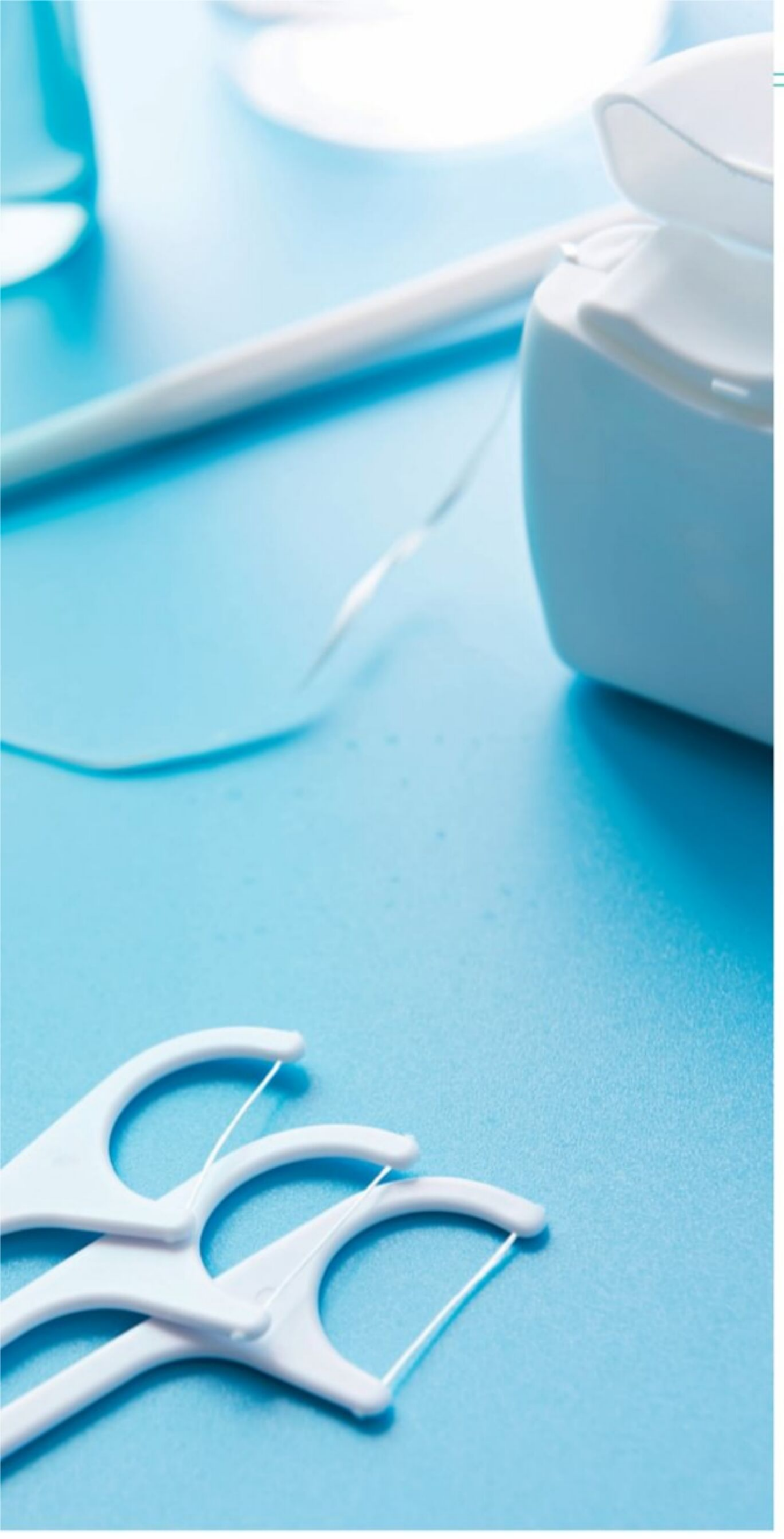
During the study's follow-up period, about 7,100 of the women developed cancer. Overall, those with a history of periodontal disease were more than three times as likely to develop esophageal cancer—and nearly twice as likely to develop gallbladder cancer. Their risk for lung cancer, skin melanomas, and breast cancer also increased by 31 percent, 23 percent, and 13 percent, respectively.

Periodontal disease is more common in people who smoke and drink, which are also risk factors for several types of cancer. And in the study, women with periodontal disease were more likely to report a history of smoking, exposure to secondhand smoke, and alcohol consumption.

But even among nonsmokers, gum disease was still associated with a 12 percent increased risk of developing cancer overall. For some types of cancer, the link to gum disease disappeared when the researchers factored out smoking habits. For other types—melanoma and cancers of the gastrointestinal tract—the connection remained.

This isn't the first research to suggest that gum disease is associated with certain cancers, but few studies—and none on older women—have calculated an overall increased risk. The researchers focused on this population because risks for gum disease and cancer both increase with age, and because a link had already been established in men.

Researchers don't know for sure why gum disease and cancer are linked, says senior author Jean Wactawski-Wende, dean of the School of Public Health and Health Professions at the State University of New York at Buffalo. But she and other researchers believe that



bacterial pathogens in the oral cavity may play a role.

"These pathogens can travel to different parts of the body through your saliva, and they come in contact with your stomach and esophagus when you swallow or end up in your lungs through aspiration," Wactawski-Wende says. When gums become inflamed and infected, pathogens—or disease-causing toxins—can also permeate the tissue and enter the bloodstream, and travel to other parts of the body as well. Previous studies have shown that these pathogens may play a direct role in the formation of cancer tumors and other inflammatory health issues throughout the body. Gum disease has also been tied to obesity, diabetes, and cardiovascular disease, but it's not clear whether gum disease contributes to these conditions or vice versa.

The study authors point out that they were only able to find an association, not a causal relationship, between gum disease and cancer risk. And it's possible that gum disease was underreported in the study, they add, since they relied on survey responses, not a medical exam.

But the large study size and the strength of their findings make a good argument for more research, they say. They're currently studying the oral microbiome—the type and variety of mouth bacteria—of women with gum disease, and they plan to see if there are any patterns or links to the cancers the women may develop in the future.

"Between this and other studies, we've seen a link between periodontal disease and heart disease, diabetes, and now cancer, so it seems to me that it would be prudent to recommend maintaining good oral health," says Wactawski-Wende. "That involves brushing and flossing, but also seeing a dental professional who can monitor and clean your teeth, and who can prevent periodontal disease or treat any cases that do arise." □

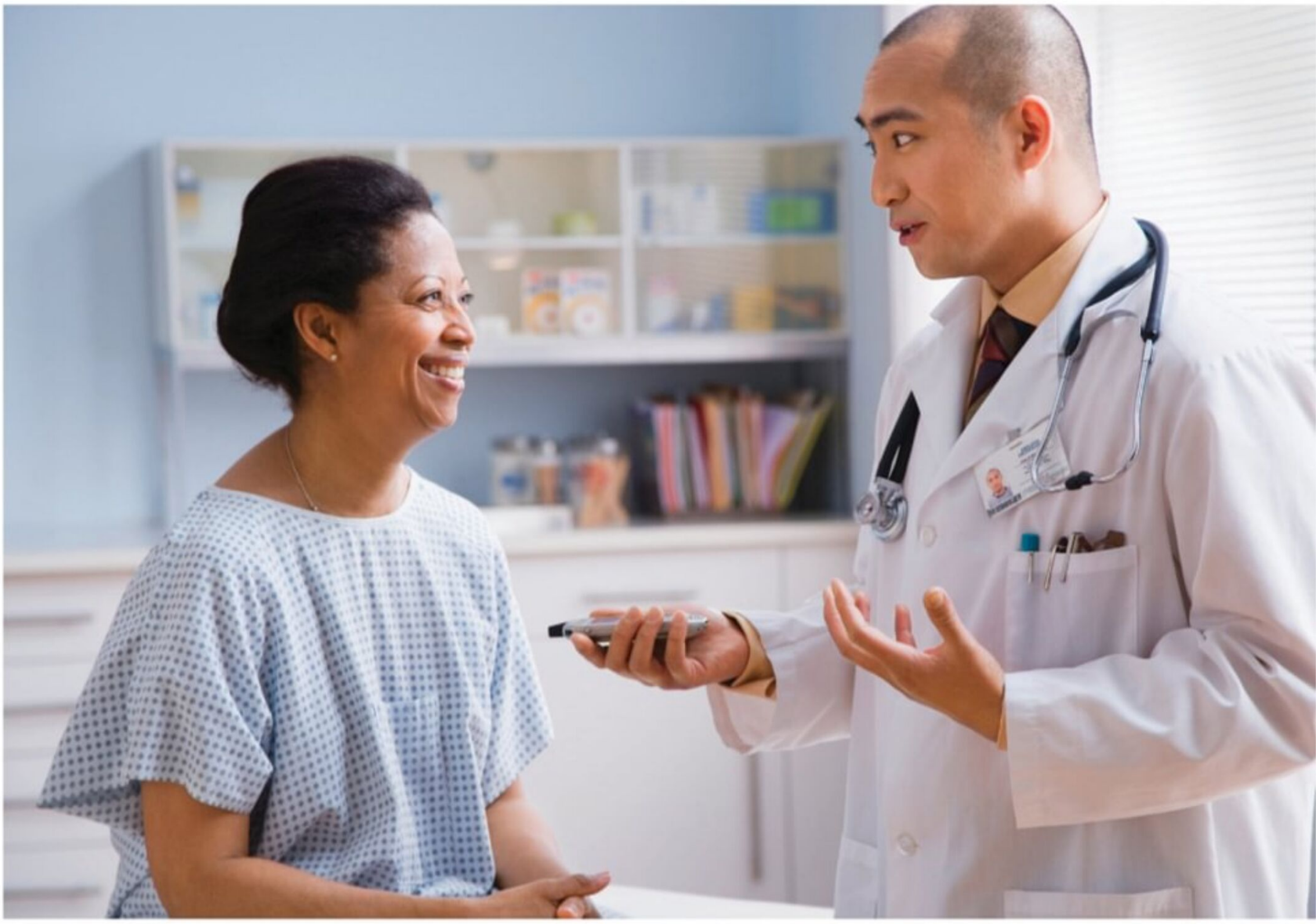
THE STATE OF THE AGING BRAIN

People are living longer than ever, and over the years, inflammation can be connected to cognitive decline.

BY GABY MCPHERSON, RDN, LDN

WHEN A LOVED ONE FREQUENTLY FORGETS IMPORTANT DEtails, loses their ability to drive safely, or mishandles their finances, cognitive decline may be underway, and it can take a devastating emotional toll. Cognition is a blend of brain processes, including learning, memory, and making judgments. Small changes in cognition can be normal in aging, but significant shifts can lead to Alzheimer's disease.

Another consequence of aging is a drop in immune function. According to a 2018 review published in *Frontiers in Cellular Neuroscience,* the nervous system, which houses the brain, nerves, and spinal cord, has open lines of communication with the immune system. Your immune system initiates an inflammatory response to guard against threats from toxins, pathogens, and injuries. Inflammation is a routine response of the human body that helps with healing. It can last for various lengths of time—seconds, hours, months, years—and the longer inflammation lasts, the more detrimental it can be to your health. Researchers and medical experts have taken great interest in unraveling the connection between inflammation and cognitive decline in trying to learn how to boost brain health to support cognition and mental sharpness for years to come.



Untreated sources of acute inflammation, such as autoimmune disorders or long-term exposure to chemicals or polluted air, can correlate with cognitive decline.

Understanding Inflammation

Swelling, redness, and warmth are signs many people recognize as inflammation, whether you're healing from a wound, a broken bone, or a bruise. "Inflammation is a natural process that is a defense mechanism for the human body," says Arif Dalvi, MD, a neurologist and director of the Memory Disorders Center at St. Mary's Medical Center, part of the Palm Beach Health Network in West Palm Beach, Florida. "Let's say you have a bacterial infection. The body will put forth an inflammation response, which means that certain white cells and cytokines will direct themselves to the area of infection to take care of it. That's the typical, natural inflammatory response."

Dalvi describes three types of inflammation: classic, chronic, and brain inflammation. "When you think of inflammation, think of a graph. The classic inflammatory response to, let's say, a bacterial infection is one in which the spike goes up and comes down right away once the infection is taken care of," he says. "The second graph is chronic inflammation, similar to arthritic inflammation, where the graph goes up, but it doesn't come back to the baseline at all. It's an extended duration over many years, or even decades, of inflammation.

"The third type of graph describes the brain cells called the microglia," Dalvi continues. "Neurons are our thinking cells and are directly involved with the nervous system, and microglial cells support these and are involved with inflammation. In this case, the graph spikes up but doesn't come down to the normal level right away. It falls short of returning to the normal level, but at the same time, it's not quite sustained, as we see in the other forms of chronic inflammation."

Inflammation is a normal, natural, intentional process in the body with pure intent to protect, but too much can become destructive. "If inflamma-

tion becomes chronic, then it leads to disease states including Alzheimer's and Parkinson's, as well as other inflammatory conditions not affecting the brain, like rheumatological inflammations or arthritis," Dalvi says. "If inflammation persists long term, it is not serving the needs of the body."

The Brain's Vulnerability

Understanding how inflammation impacts the brain starts with knowing the brain's relationship with the external environment. "What we call the blood-brain barrier acts as a shield between what's in the blood and what's in the brain, and protects us," says Gary Small, MD, chair of psychiatry at Hackensack University Medical Center and physician in chief of Hackensack Meridian Health. The word *barrier* may call to mind something impermeable, but the blood-brain barrier is not. The brain relies on a bidirectional exchange with the rest of the body for survival and healing. Supplying nutrients such as glucose for energy depends on transport across the blood-brain barrier. Further, critical cells such as lymphocytes must cross over the blood-brain barrier to help the brain fight inflammation, according to a 2021 review published in *Cellular and Molecular Immunology.* But when inflammation goes too far, the blood-brain barrier can allow too many harmful agents to pass through, especially if damage is already present from neurological disease, according to a 2017 *Brain, Behavior, and Immunity* review. "Inflammation causes changes in the brain that open up the blood-brain barrier," Small explains. Those changes "interfere with the barrier and break up homeostasis in the brain, which is a balance of different proteins, chemicals, and cells."

"Immune cells generate proteins such as activated macrophages, T-lymphocyte for example, when an infection and an inflammatory response kicks in," Small adds. "You can see correlations between elevations in those markers in the blood and cognitive problems." A 2021 review published in the *Journal of Clinical Medicine* showed that high IL-6 levels may correlate with depression or precede its development. According to a 2018 review published in *Frontiers in Aging Neuroscience,* these proteins can stimulate cranial nerves and transfer inflammation to other brain regions. Research tells us that blood-brain barrier problems are common in many neuroinflammatory and neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis, according to a 2021 review published in *Frontiers in Cellular Neuroscience.*

Inflammation and Disease

The 2018 Atherosclerosis Risk in Communities (ARIC) Cohort study published in *Neurobiology of Aging* followed 1,532 adults for 21 years in hopes of better understanding systemic inflammation and uncovering patterns in neurodegenerative changes late in life. Results showed that individuals with elevated inflammation before or during middle adulthood who maintained those high inflammation levels over the 21 years had greater white matter hyperintensity volume and reduced white matter microstructural integrity in older age compared with those who maintained lower inflammation levels. The ARIC study suggests that chronic inflammation may share in the development of abnormal white matter. That leads to tissue damage, a feature of dementia.

More longitudinal human evidence is necessary to confirm how chronic inflammation could initiate and perpetuate neurodegenerative changes. But for now, Dalvi says inflammation seems to be a contributor but not a direct cause. "Think of inflammation as a catalyst or accelerant. It's not necessarily something that directly affects these diseases," he says.

Dalvi describes an earlier study following the Rush Memory and Aging Project cohort by his colleagues at Rush University Medical Center in Chicago. "The interesting thing they found was that some people had terrible Alzheimer's pathology in the brain, but their cognitive function was not that terrible at all," he says. Conversely, "there were people who had relatively mild pathology but pretty profound dementia. And what they found was something called a cognitive reserve. So if you are, for example, highly educated and working on jobs that involve a lot of thinking, you are somewhat protected because of your cognitive reserve. It's not protecting your brain against the pathology, but your ability to handle the disease state tends to be higher." Harvard Health describes cognitive reserve as the brain's ability to improvise and find alternate ways of getting a job done. "Inflammation affects the cognitive reserve because it is damaging general areas of the brain," Dalvi says. "So indirectly, it speeds up the process that you see in Parkinson's or Alzheimer's by reducing cognitive reserve in terms of the functional capacity of the brain."

Just as there are normal levels of inflammation, there are normal parts of aging. "Sure, we lose some abilities, but we gain others; we become slower, but we have a larger picture," says Alvaro Pascual-Leone, MD, PhD, medical director of the Deanna and Sidney Wolk Center for Memory Health at Hebrew SeniorLife and co-founder and chief medical officer of Linus Health. "We have more vocabulary and more crystallized knowledge, but we may be less creative and less fluidly intelligent. So there is a balance of things we gain and lose, and overall a maintaining of cognitive function. When that maintenance doesn't happen, it's because of some underlying problem that impairs brain function and plays out in the form of inflammation."

"Brain damage through a traumatic brain injury, a stroke, a tumor—be it benign or malignant—a brain bleed, or degenerative disease by which brain cells die off like in Alzheimer's or Parkinson's can result in structural damage to the brain," adds Pascual-Leone. He describes functional alterations of the brain as seen with chronic pain or conditions such as epilepsy, where there's a misfiring of cells. "In turn, all of these things lead to a response of the brain, which is not necessarily intrinsically good or bad. The nervous system attempts to repair itself and to control the pathology and the damage." Finally, the body's attempt to protect and restore health could backfire. "Those inflammatory responses don't always accomplish the removal of the pathology or functional repair, and they sometimes become sources of irritation and damage in their own right," says Pascual-Leone.

Another risk factor for inflammation? Possibly your genes. "One gene responsible for inflammation with cognitive impairment is called the apolipopro-

tein E gene, APOE4," says Elliot Dinetz, MD, a board-certified family physician and fellowship-trained specialist in metabolic and functional medicine, and a faculty member at the University of Miami Miller School of Medicine. "Think of them as master signalers that spark massive inflammation throughout the body, but also improperly cleaving beta-amyloid plaques that accumulate in nervous tissue and contribute to cognitive decline." The National Institutes on Aging (NIA) describes the APOE4 gene as the strongest risk factor gene for Alzheimer's disease. "If you have one copy of that APOE4 gene, you're seven times more likely to develop Alzheimer's and dementia," says Dinetz. About 25 percent of people have one copy of the APOE4 gene, according to the NIA.

Essentials for Improving Brain Health

Regardless of your genetics or family history, experts stress that it's never too early or too late to get started with a healthy brain lifestyle. As Dinetz puts it, "Genes are not your destiny." A 2020 report by the Lancet Commission published in *The Lancet* addressed 12 modifiable risk factors that may cause or hasten the onset of dementia by up to 40 percent. They include obesity, diabetes, hypertension, physical inactivity, smoking, and infrequent social contact. Individually or collectively, these risk factors can increase inflammation. Managing these risk factors may require changing daly actvities and possibly adhering to a medication regimen.

In the past 40 years, obesity has tripled in the U.S., which also increases the risk for hypertension and diabetes, according to the Centers for Disease Control and Prevention. "People are chronically inflamed all the time with the standard American diet, which is highly processed and high in carbs in conjunction with high saturated fat," says Dinetz. Just as there are foods that amplify inflammation, there are foods that may help temper it. Heart-supportive eating habits such as the Mediterranean diet may prevent inflammation and help manage blood pressure. Experts agree that what's good for the heart is also good for the brain. Research shows the Mediterreanean diet may be neuroprotective, owing to its wealth of vitamins, fiber, antioxidants, and phenolic compounds. It incorporates fatty fish, nuts, seeds, legumes, whole grains, fruits, vegetables, herbs, and spices like turmeric, which may be protective against neuroinflammation. Eating well can also support healthy blood sugar levels, whether you have diabetes or not. "Alzheimer's dementia is also known as type 3 diabetes. Poor glycemic control or having an elevated fasting blood sugar is associated with a decline in brain function," says Dinetz.

RESEARCH HAS SHOWN THAT BRISK WALKING IMPROVES BRAIN HEALTH IN AGING PEOPLE WITH MEMORY IMPAIRMENT.

"Some people experience a lot of aches and pains that are not so much structural problems; it's the heightened inflammation," says Small. "Rest well and take a brisk walk. You may find that you have less pain." He recommends inviting friends along for physical activity for a dual-purpose brain exercise. "Physical exercise and the conversations during the walk will help strengthen your neural connections. And if your friend is empathic, you'll lower your stress level." Meaningful social connections are another crucial piece of the brain-health puzzle, as Dalvi, Pascual-Leone, and Small agree. Plus, exercise is ideal for whole-body health, enhancing blood pressure, managing weight, supporting blood sugar balance, and improving sleep.

"Having a good night's sleep is extremely important in terms of reducing our risk of neurodegenerative conditions," says Dalvi. "There's been a fairly recent discovery of a similar system in the brain called the glymphatic system. And this system, along with the microglia [brain immune cells], is responsible for clearing out misfolded proteins from the brain. The time that it does its most efficient job is during sleep."

Hope

Today, people can expect to live longer than earlier generations did, and that could mean more years living with cognitive decline, inflammation, and even Alzheimer's or other forms of dementia."One big challenge is that we don't have very definitive

biomarkers or good imaging techniques that document the amount of inflammation in the brain," says Pascual-Leone. He hopes to develop preventive measures and a new approach to cognitive health and well-being for assessment in the primary care setting. "For patients that I see, by the time we detect the problem, on average, they've had the disease for 15 years. So how do you detect it earlier? Well, I think we need to leverage technology—digital cognitive assessments—and they need to be optimized to be in the hands of primary care physicians."

Advancements in the study of inflammation and cognitive decline could lead to more personalized, targeted interventions. For now, many preventive measures start with the individual. You may not be able to change your age or genetics, but you can alter your lifestyle.

"Having a heart-healthy diet, getting frequent exercise, good sleep hygiene, and maintaining good social communications—all of these preventive measures really have to be emphasized," says Dalvi. We don't have to wait for cognitive decline in aging; it's not inevitable.

"What one should expect is a maintaining of cognitive functions," says Pascual-Leone. That said, if you suspect changes in your thinking and memory abilities, it's best to seek help. "There's a social stigma regarding seeking advice for these conditions," Dalvi says. "But if you're starting to have trouble from a cognitive standpoint, if you're forgetting a very familiar route or a task that was easy for you to do before, seek a neurologist, because we can work with you on the prevention side of things to get you on the right track. There's a lot we can offer, especially in the early stages, to prevent and slow these conditions." □

Research shows that a diet full of fruits, vegetables, legumes, and healthy fats can help protect the brain.

Inflammation, Depression, and Physical Symptoms

Does our anti-inflammatory response play a role in the mind-body connection?

BY AMANDA MACMILLAN

For people who suffer from depression or anxiety, being diagnosed with a physical health condition on top of their mental health issue can feel like the worst kind of luck. But recent research suggests that this type of dual diagnosis is more than just an unfortunate coincidence. Scientists are learning that seemingly unrelated psychological and physical issues may actually be closely connected.

This mysterious mind-body connection seems to be at play in a study published in the *Journal of Investigative Dermatology* that focused on the physical and mental health of people with psoriasis, an autoimmune disease that causes red patches and flaky scales to form on the surface of the skin. Depression is common among people with psoriasis, who often deal with discomfort and social stigma related to their condition.

Researchers found that psoriasis patients diagnosed with depression were 37 percent more likely to also develop psoriatic arthritis—a complication that involves inflammation of and around the joints—than those without depression.

Depression can lead to behaviors that could trigger psoriatic arthritis or exacerbate an existing case, the authors say. For someone predisposed to the disease, factors such as lack of exercise, excess weight gain, and poor diet can all affect the severity of symptoms. Yet the study authors controlled for many of these behaviors, and the association still held. This suggests that the depression itself, or the root cause behind the depression, has a direct influence on the development of psoriatic arthritis.

Elevated levels of the stress hormone cortisol might also link psychological and physical conditions beyond just psoriatic arthritis. "We know that high levels of cortisol are associated with depression, and we know that they can contribute to an inflammatory state and to conditions like diabetes and heart disease," says David Gitlin, MD, assistant professor of psychiatry at Brigham and Women's Hospital.

But there's a bright side. Treating depression and other mental health conditions (either with medication, talk therapy, or a combination of both) may help improve physical symptoms or reduce the risk of future problems, says Gitlin, especially if doing so can lower cortisol levels and other markers of inflammation. Likewise, treating physical illnesses and getting symptoms under control can help improve mental health.

For scientists, further studies and a better understanding of the body's inflammatory response may help fuel the development of treatments and preventive methods for a wide variety of diseases.

"Researchers are starting to look at anti-inflammatory agents to see if they can be helpful in treating both types of conditions," Gitlin says, citing studies that have linked cholesterol-lowering statins with a reduced risk of depression or antidepressants with a reduced risk of cardiovascular events. "We know inflammation is the singular common thread, and we're getting better at figuring out new ways to target it." ☐

COVID-19: A LASTING IMPACT

Years after the height of the epidemic, researchers are discovering how infection can potentially change the heart, even long after the virus is gone.

BY ALICE PARK

While COVID-19's effects on the lungs and respiratory system are well known, there is growing research suggesting that the virus is also affecting the heart, with potentially lasting effects.

In a presentation at the annual meeting of the Biophysical Society, an international biophysics scientific group, Andrew Marks, MD, chair of the department of physiology at Columbia University, and his colleagues reported on changes in the heart tissue of COVID-19 patients who had died from the disease, some of whom also had a history of heart conditions. The team conducted autopsy analyses and found a range of abnormalities, particularly in the way heart cells regulate calcium.

All muscles, including those in the heart, rely on calcium to contract. Muscle cells store calcium and open special channels inside cells to release it when needed. In some conditions, such as heart failure, the channel remains open in a desperate attempt to help the heart muscle contract more actively. The leaking of calcium ultimately depletes the calcium stores, weakening the muscle in the end.

"We found evidence, in the hearts of COVID-19 patients, abnormalities in the way calcium is handled," Marks says. In fact, when it came to their calcium system, the heart tissue of these 10 people who had died after contracting COVID-19 looked very similar to that of people who had heart failure.

Marks plans to further explore the heart changes that SARS-CoV-2 might cause by studying how the infection affects the hearts of mice and hamsters. He intends to measure changes in immune cells as well as any alterations in heart function in the animals, both while they are infected and after they have recovered, in order to document any lingering effects.

"The data we present show that there are dramatic changes in the heart," Marks says. "The precise cause and long-term consequences of those need to be studied more."

Previous studies have revealed a link between COVID-19 infections and heart-related problems. A large 2022 analysis of patients in the VA system—some of whom had recovered from COVID-19 and others who had never been diagnosed—showed that those who'd had COVID-19 had a higher rate of a number of heart-related risks, including irregular heartbeat, heart attack, and stroke. Susan Cheng, MD, chair of women's cardiovascular health and population science at Cedars-Sinai in Los Angeles, is studying whether there are any associations between rates of heart attack and surges of COVID-19 infections in order to better understand how the virus might be affecting the heart.

There is also early evidence that people with hypertension may be at higher risk of heart events when they get COVID-19. What connects the viral infection to the heart isn't yet known, but the body's immune system is likely a major contributor. "It's been well documented that with SARS-CoV-2, the body responds with an inflammatory response that involves activating the immune system in a very dramatic way," says Marks. "In the heart, it looks like the same inflammatory process is activating pathways that could be detrimental to heart function." But more research needs to clarify that process, according to Mariell Jessup, MD, chief science and medical officer at the American Heart Association. "If the assumption is that the infection causes inflammation, and the assumption is that the inflammation is precipitating more cardiovascular events, then how is it doing that?" Jessup says.

It's also possible that viruses can infect and adversely affect heart cells. "We're still at the tip of the iceberg with respect to understanding how COVID-19 affects health," says Cheng.

Marks is hoping to get some of those answers through animal experiments. "We hope to optimize the animal model to best reflect what we think is going on in patients," he says. "We want to study at a very, very detailed level what happens in the heart when the virus infects an animal."

Ultimately, that knowledge will help doctors better treat people who might be at higher risk of heart-related problems from COVID-19, which could in turn reduce hospitalizations and deaths from the disease. Marks has already developed a potential drug that can

address the leaking calcium if that proves to be a problem with COVID-19. He is ready and eager to test it if his animal studies justify the experiments.

But until more definitive studies clarify just how the COVID-19 virus is affecting the heart, Jessup says she would advise her patients to "control the things we know how to control," such as the risk factors that might put people at higher risk of heart disease to begin with, such as obesity, high blood pressure, and high cholesterol. And with more data emerging, if people are getting repeat COVID-19 infections, it's also probably worth seeing their doctor to get their heart disease risk factors checked as well.

"We spend a lot of time telling people that they should get vaccinated," Jessup says. "For people who have had COVID-19, we should also be making sure that they know their heart numbers and make sure they know blood pressure. We know how to prevent heart disease, so let's do the things we know how to do." □

2

EASE WHAT AILS YOU

Adopting a curated approach can help treat specific inflammatory conditions.

DECODING RHEUMATOID ARTHRITIS

This autoimmune disease attacks the joints and can trigger inflammation throughout the body. With early diagnosis and treatment, you can stay active and avoid other health problems.

BY LISA LOMBARDI

IF YOU NOTICE AN ACHY JOINT AFTER A DAY OF exercise, you may have tweaked something. But if you wake up over a period of weeks with painful, stiff joints that feel a little better once you get moving, it could be rheumatoid arthritis (RA). This painful chronic condition, which affects more than 1.3 million people in the U.S., is an autoimmune disorder: The immune system mistakes the body's own healthy cells and protein for foreign invaders and replies with an inflammatory response.

Like other autoimmune disorders, such as lupus, RA can be tricky to identify. People can go six years or longer before getting properly diagnosed, says Mehret Birru Talabi, MD, PhD, assistant professor of medicine in the division of rheumatology and clinical immunology at the University of Pittsburgh School of Medicine. And that diagnosis delay can lead to additional health problems. "Uncontrolled inflammation has whole-body effects," including contributing to cardiovascular disease and some cancers, Birru Talabi says. So it's crucial to stop that inflammation cascade.

Inflamed and in Pain

In RA, when the immune system mistakes the body's own healthy cells as a threat, it responds by attacking the joint lining (synovium). This inflammatory response—a natural process gone awry—inflames the synovium and makes the joint tender, swollen, warm, and stiff.

Someone with RA or osteoarthritis (the most common type of arthritis) may have joint swelling and pain in any joint. But there are key differences between these two types of arthritis. For one, rheumatoid arthritis often affects the small joints, such as the ones between your toes and feet, striking in a symmetrical pattern (both big toe or ring finger joints are achy, for example).

In rheumatoid arthritis, the pain and swelling tends to be at its worst right when people wake up.

Certain foods, such as dairy or gluten, can trigger rheumatoid arthritis symptoms.

The reason? Inflammatory chemicals settle in the joints overnight, explains Birru Talabi. Osteoarthritis, on the other hand, generally comes on gradually, and you joints may feel worse after you've been using them all day.

People with RA may also experience debilitating fatigue and low-grade fevers. In the early stages of the disease, though, symptoms can be subtle and intermittent (an achy but not swollen joint or two), and that makes it tricky to diagnose, says Birru Talabi. Maybe someone has symptoms but they've calmed by the time they get in to see their doctor, so they never receive a referral to a rheumatologist.

Anyone with joint pain or swelling not related to an obvious injury should visit a rheumatologist, who can diagnose or rule out the condition. They do this based on a combination of a physical examination (looking for swelling, warmth, limited range of motion, and bumps under the skin called nodules), history, blood tests looking for autoimmune markers and signs of inflammation, and sometimes X-rays and other scans.

Keep in mind that "about 20 to 30 percent of people with RA test negative on the blood tests," says Birru Talabi. She recommends keeping a symptom journal, noting when you experience discomfort and other symptoms and how they are impacting your life. The more specific you can be, the better. (For instance, you'd want to note "too stiff to walk the dog in the mornings this week, whereas I used to do a two-mile morning run every day," not just "stiff and sore"). Sometimes a person's family history provides additional clues; multiple close relatives with autoimmune disorders such as RA or lupus makes rheumatoid arthritis more likely the culprit.

Genetics play a role in some cases of RA, though researchers are still puzzling it all out. They know that variations in HLA (human leukocyte antigen) genes, which help your immune system recognize threats, are linked to a higher risk of RA. There's some evidence that environmental factors, such as smoking, can activate the genes.

A large 2019 study added to research showing smokers are at an increased risk of developing the condition. It found that smoking raises the risk of developing RA and quitting lowers it. It is possible that infections trigger RA, though more research is needed on this front, according to Kristen Mueller, PhD, vice president of autoimmune research at the nonprofit Arthritis Foundation. Experts suspect that RA has different subtypes.

As for who gets RA, you are much more likely to get it if you were born female. For reasons that aren't fully understood, the autoimmune disorder is three times more common in women than men. Women usually get diagnosed between the ages of 30 and 60. Men under 45 rarely get the disease.

This difference may be due to a genetic factor on the X chromosome, hormones, or a combination. During pregnancy, a time of great hormonal change, RA symptoms improve for 60 percent of women and get worse for 19 percent, according to a study review published in *Open Access Rheumatology*.

Next-Gen Treatments

What is crystal clear is this: Getting early treatment is essential for reducing discomfort and joint damage, and preserving flexibility. While the treatments aren't cures, they can be game changers. "A few treatments actually alter the course of the disease, so

disease progression slows," explains Mueller. These drugs, such as hydroxychloroquine (Plaquenil) and methotrexate (Otrexup), control the immune response that causes inflammation. They can take up to three months to work, and some people may notice side effects like gastrointestinal discomfort. Because they suppress the immune system, they may put you at increased risk of infection.

Biologics like adalimumab (Humira) are the latest type of disease-modifying drugs. There are a few different types, but they all work by blocking part of the immune system. They have some downsides: They are expensive and can only be given as a self-administered shot or via IV in the doctor's office, so they are generally given when other forms of disease-modifying drugs aren't working well enough.

Many people with RA also use anti-inflammatory drugs such as NSAIDs (Advil, Aleve) and COX-2 inhibitors, such as Celebrex. Doctors often recommend a combination of medications. The exact treatment is based on a few factors: how impaired someone is (there is a wide range of how severe RA can be), whether they are on other medications that might interact with drugs, and if they're pregnant or might become pregnant. It also comes down to personal preference—for instance, some people don't want an injectable because they are anxious about needles, Birru Talabi says.

While modern RA drugs work well, they're not a magic cure, experts stress. It's common for a drug to work for a while then stop doing the job, so the medication plan needs to be tweaked.

Still, thanks to the disease-modifying treatments in particular, "there's never been a better time to have RA," says Birru Talabi. Early treatment with the newer medications protects the joints long term, adds Mueller. "There used to be 'RA hands,' where the joints are all misshapen, but you don't see that anymore,' she says. "The medications are so effective that it doesn't happen."

Yet some people are uncomfortable with the idea of going on an immune-altering drug. Birru Talabi understands that hesitation, but she reminds her patients that it is not a neutral decision, because unchecked inflammation can put them at risk for multiple additional health problems. Untreated RA sets an inflammatory cascade in motion, and that can contribute to many other other inflammation-related issues, including eye and vision problems, lung disease, blood vessel issues that can damage nerves and organs, and heart problems.

Adding Healthy Moves

While you can't treat RA with fruits and vegetables, living healthy does matter. That means doubling down on the same healthy moves you already do for your heart health: Get plenty of sleep, move every day, and adapt stress management techniques such as deep breathing or mindfulness.

The exercise piece is very important. Exercise and physical therapy are very good for people with fibromyalgia, which many with RA also have. For people in a lot of pain, Birru Talab particularly likes aqua therapy and swimming, because it "takes a lot of pressure off the joints."

Eating healthy foods is also a good idea. While no diet has been shown to relieve RA symptoms or improve the course of the disease, most experts recommend an anti-inflammatory style of eating like the Mediterranean diet, with an emphasis on vegetables, fruits, fish, and olive oil and other healthy fats.

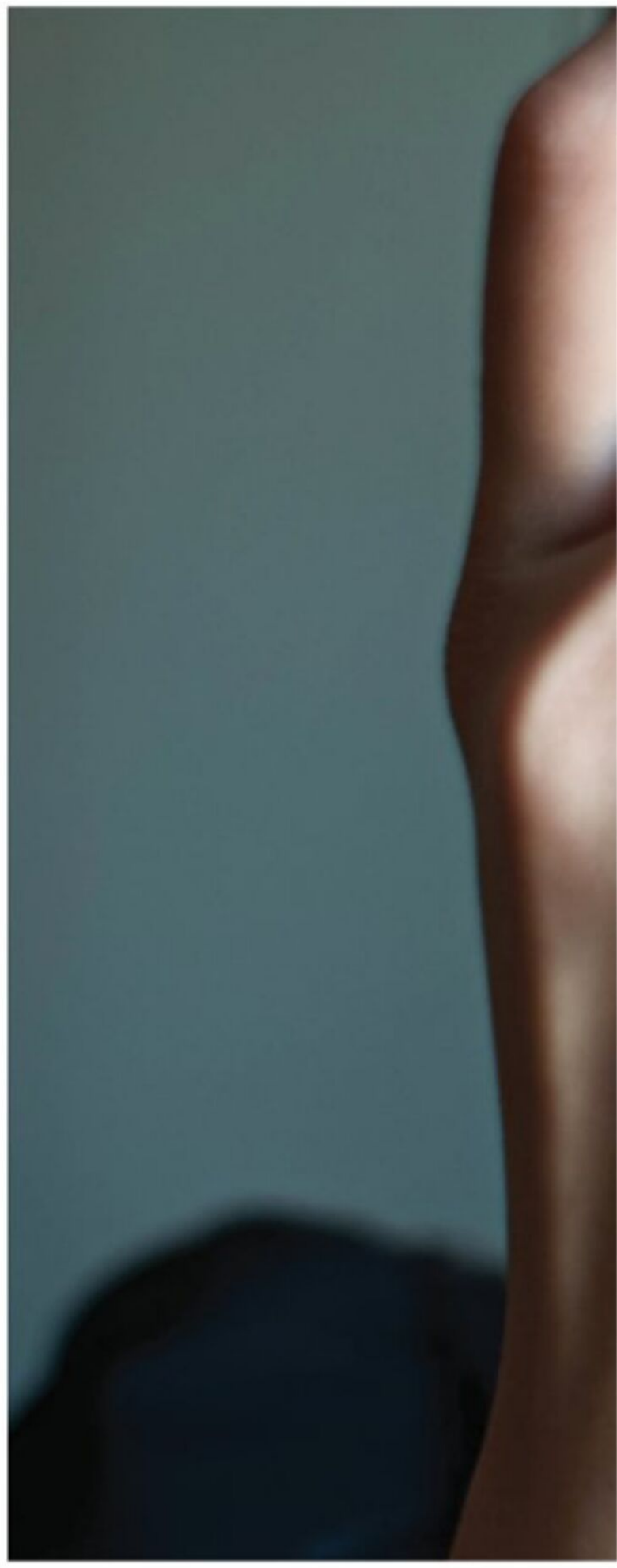
Some people with RA find that certain foods trigger symptoms, so Birru Talabi recommends paying attention to how you feel after eating in case you notice foods that cause you discomfort. (She notes that some of her patients have discovered that cutting gluten or dairy reduces their flares.)

Could alternative therapies play a bigger role in managing RA? That's also a hot research topic, according to Mueller. Researchers want to know how exercise and diet can interact with medication treatment plans to really help people. "Integrative health is being studied more and more for RA, and hopefully we'll have better answers to those questions soon," she says.

On the Bright Horizon

The biggest breakthrough on the horizon? Precision medicine. Clinical trials are underway trying to identify biomarkers, or specific proteins in the blood, that will help doctors customize treatment approaches, Mueller says. It's similar to what is already helping cancer patients.

Currently, there is a lot of trial and error when prescribing RA medications. The hope is that a person diagnosed with the disease could get blood tests that would identify the type of drugs that would work best for them. The goal is getting the disease into remission early—and keeping it that way. □



NEW HOPES FOR SEVERE ASTHMA

Asthma attacks can disrupt daily life and be deadly. Cutting-edge advancements offer a brighter road ahead.

BY MARKHAM HEID

GRAPHS AND CHARTS DON'T ALWAYS TELL THE whole story. Numbers can be deceiving. But anyone who looks at U.S. trends in asthma mortality can see, without squinting, that things are moving in the right direction.

A 2019 analysis in the *American Journal of Respiratory and Critical Care Medicine* found that from 1999 to 2015, asthma mortality fell by 43 percent. "The decrease in asthma-related mortality was consistent in both sexes and in all race groups, with the largest decrease in patients older than 65 years," the authors concluded. Figures from the U.S. Centers for Disease Control and Prevention indicate that these positive trends have continued through 2019, and data coming from the U.K. and Europe tell a similarly happy tale.

"What I see in the clinic today is completely different than it was 10 years ago," says Christopher Brightling, PhD, a clinical professor in respiratory medicine at the University of Leicester and a senior investigator at the National Institute for Health and Care Research in the U.K. "The treatment space is looking really positive, and with the newest drugs, I would anticipate responses to be even better."

Biologics, he and others say, are leading the way in the fight against severe asthma. These drugs work by manipulating the activity of genes or cells, and they have been life-changing for many patients. New

advancements in inhaler-based medicines and connected technologies are other bright spots, and some health systems are moving their care teams out of the clinic and into community settings in an effort to reach underserved populations.

Together, these and other new advancements are producing real and measurable improvements in patient access and outcomes. "It is really a very exciting time in asthma research right now," says Derek Chu, MD, PhD, an assistant professor of medicine and a researcher in allergy and clinical immunology at McMaster University in Canada. "There's a lot in development for both mild and moderate-severe asthma."

What's New in Biologics?

In 2003, the U.S. Food and Drug Administration (FDA) approved the first biologic for the treatment of severe asthma. That drug, omalizumab, is a monoclonal antibody therapy that works primarily by reducing blood levels of IgE, an immune system antibody that contributes to airway inflammation among people with severe asthma.

Although omalizumab was revolutionary, experts say the past few years have witnessed the arrival of newer and better biologics that have all but eradicated the burden of severe asthma for most patients. "These have been totally transformational," says David Jackson, a respiratory medicine specialist at

King's College London. "Since 2017, a new biologic has been added to our armory on almost an annual basis, and the number of patients with uncontrolled asthma has gotten smaller and smaller."

Whereas the first biologics blocked IgE, the latest drugs in this category target—with greater and greater precision—the specific immune pathways and cells that drive asthma-related inflammation and symptoms. "Cells called eosinophils are a hallmark of severe asthma, and these newer biologic therapies can dampen down their production and related pathways in a much more targeted way," Jackson says. He uses a military analogy to highlight the effectiveness of the newest biologics. "These are like precision-guided laser bombs, as opposed to the old B-52s dropping bombs from 50,000 feet and just hoping for the best."

Some of the newest biologics take aim at two specific immune system proteins: thymic stromal lymphopoietin (TSLP) and interleukin 33. "These two activate cells in the airways, which leads to a release of all these [inflammation] players," Brightling explains. Because these two are farther "upstream" than some of the pathways targeted by older biologics, mellowing their activity may produce broader benefits, he says.

Biologics do come with downsides. For one thing, they're expensive. They often cost around $30,000 a year in the U.S., Jackson says, and they are not always covered by insurance. Also, in the past their administration required regular office or clinic visits. Biologics are traditionally delivered via injection anywhere from once every two months to once every two weeks. However, the coronavirus pandemic helped shift the use of these drugs away from the clinic and into the home. "There's been a big push to self-administration," Jackson says. "What we normally do now is to start in the clinic—give the first one to three administrations here—and then go to home administration when it's clear that the patient is doing well."

Despite any lingering financial and logistical hurdles, the benefits provided by biologics are often profound. The latest and greatest biologics work so well that many patients are effectively relieved of the burden of severe asthma attacks or symptoms—something that would have seemed unbelievable just a decade ago.

Unfortunately, not everyone who would benefit from these drugs is getting them. "Awareness of this medicine is not what it should be," Jackson says. "A lot of patients continue to have asthma attacks and their doctor hasn't picked up on the fact that there are newer therapies." If every clinician who treats severe asthma were up to speed on these drugs—and if everyone who truly needs them had access to these medicines—it's possible that virtually every person with severe asthma could avoid the worst symptoms, he says.

'Smart' Inhalers

Every asthma specialist knows that getting patients to reliably take their medicine can be a struggle. Particularly among young people with severe asthma, adherence is often poor. A 2018 study in the *European Respiratory Journal* found that even after special educational courses in inhaler use and disease management, only 63 percent of people with severe asthma adhered to their treatment plan.

"I think one of the biggest challenges, especially with severe asthma, is that patients feel fine a lot of the time, and it's difficult to remember to take a medication every single day if you're feeling good," says Ruchi Gupta, MD, a professor of pediatrics, preventive medicine, and medicine (allergy and immunology) at Northwestern University's Feinberg School of Medicine and Lurie Children's Hospital. Other experts say that pricey biologics might be needed far less if more patients with severe asthma reliably took their inhaled corticosteroids.

There's a new solution to this problem: smart inhalers that can notify patients or their care team when doses are missed. For a 2021 study published in *Pediatrics,* Gupta and her colleagues examined the usefulness among children with asthma of inhalers equipped with Bluetooth-connected technologies. The inhalers notified a child's care team if they missed their daily doses several days in a row, or if they took too many rescue doses in a single day. After 12 months of follow-up, treatment adherence had increased by 17 percent, and measures of asthma-symptom burden had likewise improved, the study found. "Patients felt like someone was looking out for them and taking care of them," Gupta says.

Some of these smart-inhaler technologies are already available (though usually not covered by insurance). For example, patients can buy inhaler sensors that will remind them when to take their meds. Some health care systems have also set up office notifications similar to the type Gupta and her team

Smart inhalers can notify patients or their care team when doses are missed.

studied. But for the most part, these new technologies are not yet widely deployed.

"My dream is that every time a patient uses their inhaler, this information would go straight into their electronic medical chart," Gupta says. "I know some groups are working on that."

The Road Ahead

There's a lot more going on in the field of severe asthma care. For a 2021 study published in *JAMA*, Chu found that triple-drug therapy—adding a third medication to the common two-drug combination of corticosteroids and bronchodilators—led to a lower incidence of severe attacks among patients who use inhalers.

Although the future looks bright, Chu says that more work lies ahead. "The main issues are the critical need for head-to-head studies of active drugs or management approaches, rather than purely placebo-controlled studies," he says. This work could further clarify the best treatment approaches.

However, life for many people with severe asthma has never been better. "Many patients almost feel like they don't have the disease anymore," says Jackson. "They stop having attacks, stop showing up in hospitals, and can function without asthma interfering in their life." That's worth celebrating. □

THE DIABETES LINK

Inflammation makes people with diabetes more vulnerable to heart disease.

BY ELAINE K. HOWLEY

IF YOU'VE BEEN DIAGNOSED WITH DIABETES, KNOW THAT you've got plenty of company. The American Diabetes Association (ADA) reports that in 2019, the most recent year for which data is available, 37.3 million adults in the U.S.—about 11.3 percent of the population—had the chronic condition, and that number continues to grow.

Type 1 diabetes develops when the body isn't able to produce insulin, and type 2 occurs when the body doesn't use insulin correctly. Type 2 is the most common form of diabetes, and when it's uncontrolled, a person's blood sugar can jump to dangerous levels that require medical treatment.

Over time, elevated blood-sugar levels spell trouble for the entire body, says Joshua Joseph, MD, an endocrinologist at the Ohio State University Wexner Medical Center in Columbus and an investigator with the ACCELERATE Research Group, which is working to prevent and treat diabetes and cardiovascular disease. "High levels of blood sugar damage the small and large vessels in the body," including those around the heart, leading to heart disease, he says. Elevated glucose can also harm the nerves that control the heart.

Indeed, diabetes is correlated with a heightened risk of major

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adverse cardiac events, including stroke, heart attack, and death. People with diabetes are twice as likely to have a heart disease or stroke as those who don't have diabetes, and it's more likely to happen at a younger age. Plus, the longer people have diabetes, the more likely they are to develop heart disease, according to the National Institutes of Health. Here's a look at what to know, plus expert tips on keeping your heart—and whole body—healthy.

The Connection Between Diabetes and Heart Disease

People with type 1 diabetes may have a lower risk of heart complications than do those with type 2. That's because they're less likely to be overweight or obese, which can increase the risk of heart problems. There's also more research on type 2, because it's the most common form of the disease.

Despite some variations between type 1 and type 2 diabetes, for individuals with these conditions, cardiovascular disease is the No. 1 cause of death, says Robert Gabbay, MD, PhD, chief scientist and medical officer of the ADA. It's not entirely clear why and how diabetes and heart disease are connected, but there are likely several factors involved.

As Gabbay says, "People with diabetes are more likely to have other comorbidities that independently increase the risk of heart disease." Conditions such as hypertension (high blood pressure), hyperlipidemia (high cholesterol), and obesity can increase the risk of heart disease. "When you start adding those together, the risk starts multiplying," he says.

Diabetes can create an inflammatory environment in the body, which Andrew Freeman, MD, a cardiologist at National Jewish Health in Denver, calls "a milieu" that can lead to other chronic problems. The high blood sugar that diabetes creates in the body can "lead to a variety of inflammatory states and microvascular disease, or small blood vessel disease," Freeman explains. "The very same environment that helps create diabetes helps to create cardiovascular disease, and vice versa." Systemic inflammation stemming from high blood sugar can lead to blood clots, stroke, and heart attack.

Obesity is related to insulin resistance, which means your muscles, liver, and fat cells don't respond well to insulin and aren't able to use the glucose in your blood to fuel their functions. Insulin resistance, sometimes called prediabetes, can develop into type 2 diabetes. "Insulin resistance is associated with all sorts of other bad things, and one of these is inflammation," Gabbay says.

The risk to the heart posed by diabetes is clear, Gabbay says, but the reverse is less clear—it's not always the case that having heart disease puts a person at higher risk of developing diabetes. That said, "it's not unusual. I've seen this many times, that someone comes in with a heart attack and they're also diagnosed with having diabetes. They just never knew it." In these instances, he says, diabetes likely contributed to the heart attack.

If you have diabetes, it's important to be familiar with the symptoms of heart disease. According to the ADA, they include chest pain, shortness of breath, fainting, a rapid or slow heartbeat, numbness in your legs, exhaustion, nausea and vomiting, and pain in one or both legs.

Depending on your symptoms, your doctor might order tests such as an electrocardiogram, which checks the heart's electrical signals, or cardiac computerized tomography, which supplies 3-D images of your heart and blood vessels.

Reducing Risk

Fortunately, there are many ways to reduce risk and limit progression of diabetes and heart disease, Gabbay says. The ADA has partnered with the American Heart Association to tackle the issue via a program called Know Diabetes by Heart. It aims to increase awareness of the connection between diabetes and heart disease and to provide patients with resources to keep themselves healthier.

It's clear that treating diabetes appropriately can limit the risk of cardiovascular disease, Joseph says. This means "controlling the ABCs of diabetes."

A stands for A1C, a measure of blood-glucose control over time. Keeping that level at your goal, which for most people is below 7 percent, means your diabetes is well managed and will do less damage to the body. This is usually accomplished through diet, exercise, and medication. If you're not sure what your A1C goal should be, ask your doctor.

B stands for blood pressure. Controlling hypertension, often called the silent killer because it seldom produces symptoms, is a major component of managing heart disease. If your blood pressure is too high, it can cause a heart attack or stroke, as well as kidney damage and other health problems.

C stands for cholesterol, which is a type of fat found in the blood. Keeping blood vessels clear of

the plaque that can build up when cholesterol levels rise helps prevent heart attack and stroke.

S stands for "stop smoking," which doctors widely recommend. If you smoke, stop as soon as possible: It's a major risk factor for diabetes and heart disease, as well as many other chronic conditions. Quitting smoking helps lower your risk for heart attack, stroke, and diseases of the nerves, kidneys, and eyes.

Similarly, consuming too much alcohol can be a problem, as it can elevate blood pressure and lead to heart failure or stroke. One drink per day for women and up to two for men is typically considered safe, but keep in mind that "one drink" means a 12-ounce beer, 5 ounces of wine, or 1.5 ounces of 80-proof spirits.

Medication

A wide variety of medications are available to help control diabetes and slow its progression. They may also help manage your risk for heart disease. Insulin is the most common; it replaces the insulin your body can't make or isn't making enough of to control blood sugar. Metformin is another widely used medication that limits how much carbohydrate the intestines can absorb and boosts insulin sensitivity to help the body better manage blood-sugar levels. Other medications, such as amylinomimetic drugs that are injected before meals, can slow the rate of digestion, lowering your blood-sugar levels.

Two new classes of medications show promise in treating glucose levels in people with type 2 diabetes, Gabbay says. These medications—GLP-1 receptor agonists and SGLT-2 inhibitors—have been shown to have a significant impact on lowering the risk of heart disease and stroke. Both help lower glucose levels and may support weight loss and blood-pressure reduction.

Gabbay says these new medications "have been shown to reduce heart disease, cardiovascular mortality, and all sorts of cardiovascular-related issues, but they're underutilized." People with type 2 diabetes and poor blood-glucose management would benefit the most, and of that group, only about 15 percent are using these medicines.

Managing diabetes can help prevent heart disease. However, for people who already have both conditions, treatments that address any damage that has occurred in the heart or blood vessels are important and should be delivered alongside blood-sugar management. Individuals with both conditions will likely also need to control blood pressure and cholesterol levels, which can be achieved through medications as well as diet and exercise.

RESISTANCE TRAINING AND AEROBIC EXERCISE BOTH HELP LOWER INSULIN RESISTANCE IN PREVIOUSLY SEDENTARY OLDER ADULTS.

Diet and Exercise

Exercise is a key way to control type 2 diabetes and support a healthy heart. For people with obesity, losing weight is typically advised, and exercise may help you achieve that.

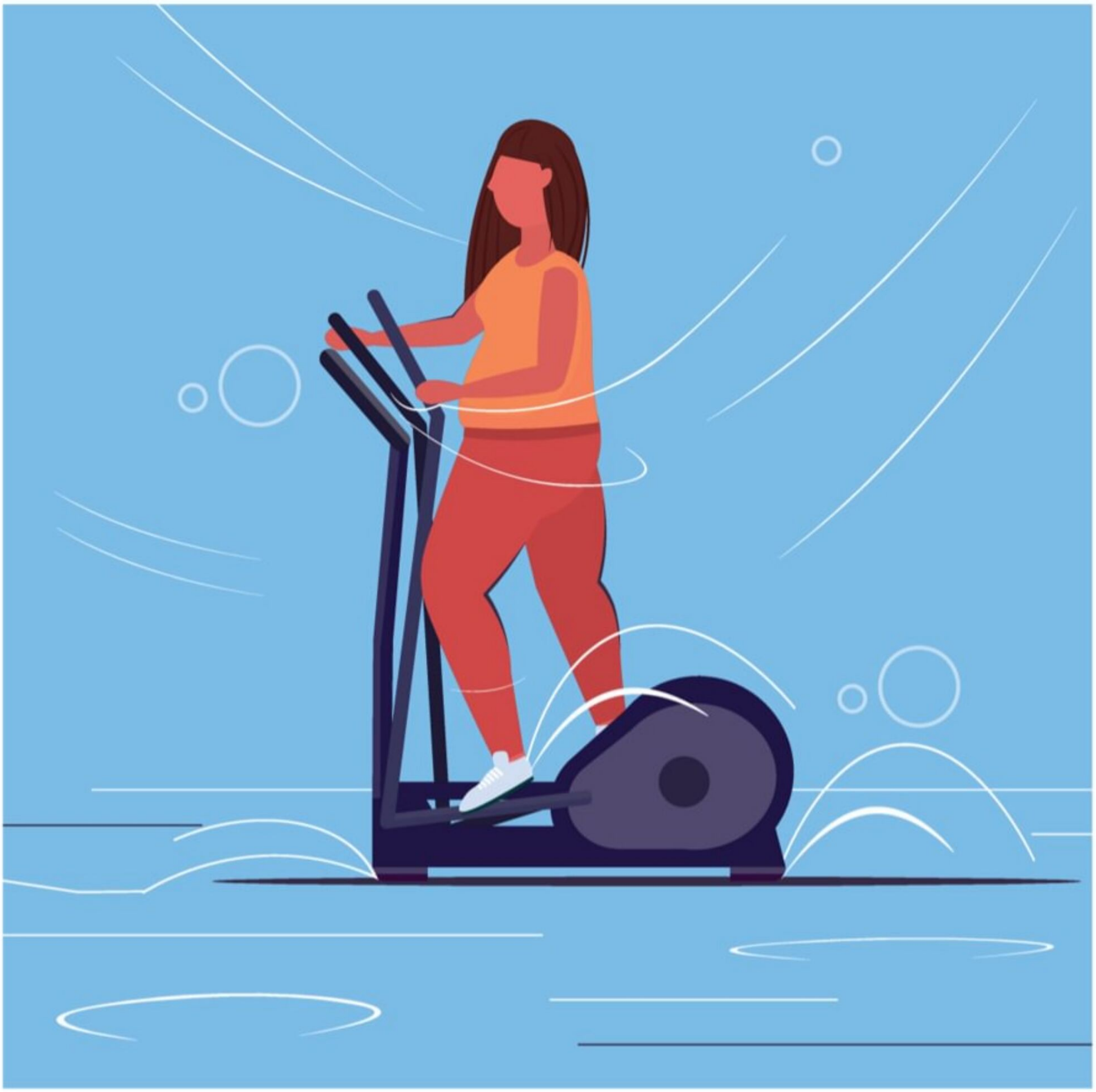
Eating right is also important, a fact that was first emphasized in the 1940s. "Back then, there weren't a lot of treatments for diabetes or heart disease," Freeman says.

Today, we know more about how food contributes to the development of chronic disease or helps improve overall health. Doctors often advise a plant-based approach that's low in unhealthy fats.

One of the most widely recommended diets for overall health and wellness is the Mediterranean diet, which features mostly vegetables and fruits, whole grains, some fatty coldwater fish, and limited dairy and meat. The DASH diet, which stands for Dietary Approaches to Stop Hypertension, is also a good plan for heart health. It's rich in vegetables, fruits, and low-fat dairy, and it also limits sodium.

No matter which eating plan you adopt, Freeman says, there are five things he tells people who are trying to control their diabetes and, in turn, protect their heart. Aim to get 30 minutes per day of moderate or vigorous exercise, and make it a regular habit. "You want to be in a zone where it's hard to talk while you're exercising," he says.

Following a predominantly low-fat, whole-food, plant-based diet—one that's rich in fruits and vegetables, without too many processed foods—is the



way to go. Skip refined oils, processed meats, and fried foods, as these can all contribute to higher cholesterol levels.

Many people with type 2 diabetes have sleep problems because of unstable blood-sugar levels, according to the Sleep Foundation. If you're finding you can't get enough sleep, talk to your doctor. "Seven hours a night of uninterrupted sleep is an incredibly powerful way to reduce cardiovascular disease," Freeman says.

Long-term stress can increase blood-sugar and blood-pressure levels. "High-stress environments raise blood pressure, cholesterol, and risk for cardiovascular events," Freeman says. Try yoga, meditation, deep breathing, or spending time in nature to cope with your stress.

Connecting with others can be a powerful way to stay healthy, too. "A strong social network reduces the likelihood of a cardiovascular event," Freeman says. A diabetes educator can also help you better understand the steps necessary to manage diabetes while protecting your heart. ☐

MANAGING IBD

AGING SYSTEMS

During the aging process, treating IBD becomes more challenging. The latest treatments offer an active quality of life.

BY KATHERINE HARMON COURAGE

INFLAMMATORY BOWEL DISEASE (IBD) HAS LONG BEEN thought of as an ailment of middle, or even young, adulthood. The chronic illness—which includes Crohn's disease and ulcerative colitis, and can cause abdominal pain, diarrhea, bleeding, and decreased quality of life—impacts about 3.1 million people in the U.S. However, it is far from a disease only of the young and middle-aged. More than a quarter of people with IBD are elderly, a figure that is projected to climb to 30 percent by 2030, according to a 2021 article in *Gastroenterology & Hepatology*.

Even more underappreciated is the growing population of people who are diagnosed with the disease after they turn 60. Whereas IBD was once taught as a disease with two spikes in onset—20s to 30s, and 40s to 50s—doctors are learning there is a third spike that begins later in life. "Now we know you can be 75 and get IBD," says Simon Hong, MD, a gastroenterologist and IBD specialist at NYU Langone Health.

Regardless of when the disease starts, however, understanding—and treating—IBD in older adults comes with its own set of challenges and intricacies.

Differences in Older Adults

Hundreds of thousands of people whose IBD was diagnosed earlier in their lives are now living with the disease in older age. For many, that means living with the damage the disease has done to their intestinal tract, and sometimes with the altering impacts of surgery done to manage it, such as ostomy pouches or increased incontinence. Not to mention continued flare-ups.

It used to be commonly thought that disease activity tapered off in older age, and some people do find that their IBD becomes inactive later in life. But that isn't always the case, says Cleveland Clinic gastroenterologist Jessica Philpott, MD. "I certainly see some patients who develop more aggressive disease as they advance in age," she says.

For individuals who get IBD after they turn 60, the disease can look somewhat different than for those who have had it for decades. Whereas younger Crohn's patients can have damage in any part of their intestinal tract, in older-onset cases it more often primarily affects the colon.

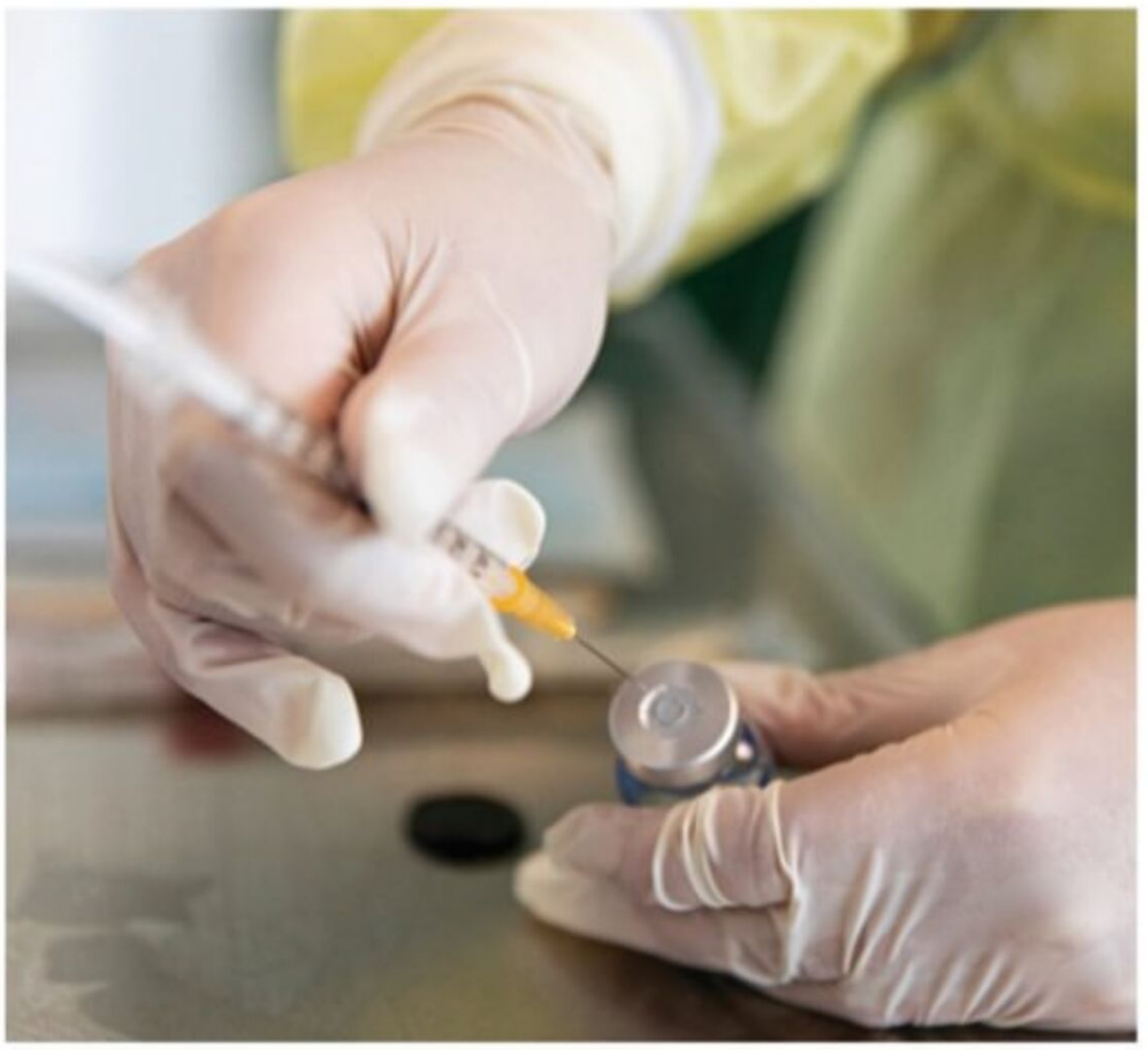
As people age, diagnosing a new case of IBD also gets more challenging. There are numerous, more common reasons an elderly person might experience bloody diarrhea, for example. This alarming symptom is one of the first reasons for IBD evaluation in a younger person. But for someone in their 60s or older, doctors often need to rule out a host of other conditions—including infection, ischemia of the colon, other forms of colitis, diverticulitis, and cancer—before they look into IBD as a potential cause.

And because older adults have often already faced more health issues, they might not seek medical help as promptly. Crohn's disease in particular can be trickier to pinpoint than ulcerative colitis, as it might present as intermittent abdominal pain and weight loss, which aren't uncommon in older adults generally. These factors can sometimes delay proper diagnosis, and thus effective treatment, by years.

Gil Melmed, MD, director of inflammatory bowel disease clinical research at Cedars-Sinai Medical Center in Los Angeles, recounts the story of one patient who is now 84. She had been hospitalized numerous times for abdominal pain and bloody diarrhea. Doctors repeatedly diagnosed her with diverticulitis and treated her with antibiotics. Her symptoms would get better for a while and then return. Then the antibiotics led to additional complications, including a dangerous C. difficile infection. When Melmed first saw her, after yet another hospital admission, he realized she wasn't suffering from diverticulitis at all but Crohn's disease.

Hong has seen this misdiagnosis cycle countless times. "Doctors do have to always remember to have IBD on their list" for people who are older, he says.

The rate at which people are getting late-onset IBD appears to be increasing, likely because of environmental triggers such as air pollution, which makes being vigilant even more important.



Other Complexities

At its core, IBD is a disease of chronic inflammation. Aging itself is also linked with increased inflammation, a connection that has given rise to the term *inflammaging*. So aging patients with IBD are at even greater risk for many of the classic inflammation-linked health outcomes, including cardiovascular disease, cancer, obesity, skin issues, arthritis, and skeletal muscle loss.

Experts caution that some common

health complaints may look similar to those of older adults without IBD, but in reality the IBD has triggered a different issue. For example, joint pain in an older patient might first appear to be osteoarthritis, but if they have IBD, it may well be a different form of arthritis altogether. Older IBD patients also have increased risks for other conditions, including osteoporosis, colon and skin cancers, blood clots, and general physical deconditioning.

The long list of potential health issues increases the importance of standard preventative care, including good nutrition and exercise, as well as simple things such as routine immunizations, Melmed notes. Until recently, many vaccines for older adults contained live virus, making them riskier to mix with some IBD therapies. This is no longer the case, Melmed says, and in fact, because so many IBD treatments suppress the immune system—and aging itself is also associated generally with an increased risk of infections—it is especially important for these patients to get regular vaccines for illnesses such as pneumonia.

There are still many complex unknowns about the aging body as it is impacted by IBD, and vice versa. For example, we don't yet know much about how aging with IBD looks different for women going through menopause and afterward, and what role menopause treatments might play in the course of the disease. Some small studies have found a modest protective role for estrogen-replacement thera-

pies for IBD disease activity, but the answers aren't yet definitive. "We really need more data in this area," says Sunanda Kane, MD, who specializes in IBD and women's health at Mayo Clinic in Rochester, Minnesota.

But even something as big as menopause can be missed—or misinterpreted—when doctors are overly focused on a patient's IBD and its treatments. Kane recalls one 57-year-old patient who was on a newer monoclonal antibody therapy for her ulcerative colitis. One day the patient told her primary-care doctor that she was having fevers and "confusion." The doctor concluded that she was likely suffering from a rare brain infection as a result of her IBD medication, told her to discontinue the medication, and referred her to a neurologist.

While the patient waited anxiously for her neurology appointment, she called Kane to ask what other IBD medication she could take instead. Kane listened to the patient's story and realized that her symptoms were those of menopause. Back on her previous IBD treatment and estrogen-replacement therapy, the patient ended up doing well, Kane reports. But the incident served as a reminder that the presence of IBD can cloud the assessment of a patient's full picture, especially when big health changes come up, as they so often do during the aging process.

One thing that has become clear as more people live with IBD into older age is that when evaluating patients for IBD and their treatment prospects,

it's not just about age. Experts now advocate basing decisions on one's frailty score over chronological age. And like inflammation, the combination of aging and IBD increases the odds of frailty, which puts someone at greater risk for poor health outcomes.

The Challenges of Treating Elderly Patients with IBD

As we age, treating illness tends to get more challenging. There are more comorbidities, a lengthening list of medications, and an older person's overall health to take into account. These factors become even more important when considering IBD therapies. "Anything we do, from procedures to treatment, it's different for someone that's older," says Philpott.

Once the disease advances to a particular state, doctors often look to surgery to remove the damaged part of the intestinal tract. This, however, is not always an option for extremely frail patients with IBD, no matter their chronological age. The disease, of course, can typically be managed well with medication. But there are some common pitfalls, warn specialists who work with elderly IBD patients.

LIKE INFLAMMATION, AGING AND IBD PUT PEOPLE AT GREATER RISK FOR POOR HEALTH OUTCOMES.

One of the biggest concerns in pharmaceutical treatments for older IBD patients is susceptibility to infection, because nearly all IBD drugs in some way tamp down the immune system, which is already on the decline as the body ages. But this concern, experts say, can lead to vast undertreatment of the condition—or treatments with even riskier forms of drugs.

For decades, corticosteroids have been a standby of IBD therapy. And they are still indicated for short-term treatment of mild to moderate disease flare-ups, particularly in younger adults. But their long-term use, especially for older adults, is less effective than other options and can actually bring higher risks, including for hypertension, diabetes, bone loss, infection, osteoporosis, and overall mortality.

Nevertheless, some 30 percent of elderly IBD patients have been prescribed steroids for more than six months at a time, according to a 2015 study published in *Inflammatory Bowel Diseases*. Part of the reason, says Hong, is that because of these drugs' long history, "they're seen the 'safe' option. I would argue that rather than being on steroids for a long period of time, it would be much better to be on one of the new biologics."

In the past several decades, small molecule "biologics" have entered the scene as a newly established treatment for IBD. Particularly effective are antitumor necrosis factor agents. Some clinicians are reluctant to prescribe these medications because they are known to increase the risk of some cancers, such as lymphoma, especially in older adults. Some doctors even recommend a patient have surgery—which, of course, comes with its own not insubstantial risks for older individuals—before trying biologics.

Melmed's 84-year-old patient who was finally diagnosed with Crohn's disease was immediately started on biologics, and has yet to have another flare-up. Melmed acknowledges that there are risks with these drugs for older patients, but he looks at the larger picture of "how to best benefit a patient," he says. "There's no risk-free option. Just because somebody's older, we certainly don't want to deny them the potential benefits of an effective therapy." As part of that approach, Melmed advocates assessing not just patients' intestinal health but also their environment and well-being.

Younger people with IBD are known to have higher rates of depression and greater challenges navigating normal life because of the unpredictability of attacks. There's no reason to think this would be different for people who are older. But depression can be more difficult to spot in an elderly patient if it isn't screened for, and being fairly homebound or lacking social support might be more accepted as normal.

It doesn't have to be that way, experts agree. "As doctors, we're always focused on inflammation," Hong says. "But in reality, what matters is: What does this older patient want to do? Do they want to travel? Ride a bike around the park?

"Just because they're older doesn't mean they don't deserve the same quality of life," he adds. "Don't settle for less." ◻

MANAGING IBD

HOW YOUR DIET CAN HELP

From Mediterranean-inspired eating patterns to exclusion plans, food can help reduce IBD symptoms.

BY MICHAEL O. SCHROEDER

"'DOCTOR, WHAT SHOULD I EAT WHEN LIVING WITH IBD?' IS likely the most frequently asked question following diagnosis," says Maitreyi Raman, MD, an associate professor of medicine at the University of Calgary.

Raman, who's a gastroenterologist, physician nutrition specialist, and researcher, has closely studied the topic and has reviewed the available evidence for dietary patterns that may be of benefit (or not) to patients.

IBD includes Crohn's disease, which can cause inflammation in any part of the digestive tract and commonly affects the small intestine; ulcerative colitis, limited to the large intestine, or colon, and rectum; and indeterminate colitis, which has features of both Crohn's and colitis. Symptoms for all forms of IBD include diarrhea, abdominal cramping and pain, fatigue, and unintended weight loss.

Given IBD's life-disrupting nature, patients are often highly motivated to try different therapies that might bring relief, including making changes to their diet. "The role of diet as a risk factor and therapy for IBD has been of great interest to patients," says Raman, who co-authored a review of diets for IBD published in *Clinical Gastroenterology and Hepatology* in March 2021. Those findings indicate that exclusive enteral nutrition (no solid foods) is the most

well-supported approach but isn't realistic for everyone. Other plans, such as the specific carbohydrate diet, can also be helpful.

Unfortunately, there's a relative dearth of research on the best diet for IBD. Still, evidence is growing. Over the past decade, the science and understanding of the gut microbiome, which comprises trillions of bacteria (helpful and harmful), have evolved, Raman notes. An imbalance of bacteria in the gut can cause a host of health problems and may contribute to IBD. And diet can make a big difference. Recent high-quality randomized controlled trials have found that changes in diet improved IBD symptoms, reduced gut inflammation, and enhanced patient outcomes, Raman explains.

Before diving into options for what you might put on your plate and in your body if you have IBD, know that experts emphasize that dietary changes aren't a wholesale substitute for medical treatment.

"Diet is one of many therapies," says James Lewis, MD, associate director of the Inflammatory Bowel Diseases Program at the University of Pennsylvania Perelman School of Medicine. "While a diet-based strategy may be preferred and practical for some patients, it may be much harder to implement for others." Certain diets for IBD are quite restrictive, and any significant changes in eating patterns can be challenging to sustain. Still, many patients—especially those with mild to moderate disease—look to diet as one therapy option for IBD.

Experts recommend that IBD patients seek professional help in order to develop a personalized eating plan. Therezia Alchoufete, RD, lead dietitian for UPMC Total Care at the University of Pittsburgh, stresses that dietary choices need to be tailored to the individual.

Consider your goals not only related to IBD but also for your overall health, and make sure the focus is on what you can eat, not just what you're eliminating. Alchoufete talks to patients about making thoughtful choices while looking to increase variety and nutrients.

"My goals for each patient would be to begin building this positive relationship with food—really understanding which foods can help them feel good," she says.

Exclusive Enteral Nutrition

The most widely studied and data-supported diet for IBD—and Crohn's in particular—is an all-liquid, formula-based meal-replacement diet. It's called exclusive enteral nutrition, and it's typically prescribed and overseen by doctors. Most commonly recommended for children, it can be followed by drinking a speciality formula prepared by a doctor or administered via a feeding tube inserted through the patient's nose and into the stomach.

There's strong evidence to show that exclusive enteral nutrition leads to reduced inflammation and improved healing, and it's comparable to treatment with steroids in helping patients achieve remission from Crohn's, which means the disease is no longer active. It also works relatively quickly. Short-term exclusive enteral nutrition programs are designed to induce remission in six to 12 weeks.

However, it's primarily been studied in children,

not adults. And there's an even more obvious downside: It's challenging to stick with from a quality-of-life standpoint, since it requires entirely eliminating normal food, says Ashwin Ananthakrishnan, MD, a gastroenterologist in the Digestive Healthcare Center at Massachusetts General Hospital.

Crohn's Disease Exclusion Diet

Successful IBD diets eschew the traditional red-meat-heavy, sugary, processed Western diet that wreaks havoc on gut health. Research suggests the shift toward that way of eating bears much blame for increases in IBD rates—even in countries like Japan, where the Western diet has been adopted as well.

To counter that, the Crohn's disease exclusion diet seeks to cut out common Western diet staples, such as processed meat, artificial sweeteners, and alcohol, which may affect gut health. Evidence from high-quality comparative trials demonstrates the diet's effectiveness in relieving symptoms and reducing inflammation—and it could start to work within three to six weeks.

But as its name indicates, the Crohn's disease exclusion diet is highly restrictive. In the 2021 study examining the approach, participants were only allowed to have chicken breast, eggs, and partial enteral nutrition—liquid formula for a portion of their calories—as sources of animal protein, and they were limited to certain fruits and vegetables, for the first six weeks. The second six-week phase involved the gradual introduction of almost all fruits and vegetables while restricting beef and legumes and allowing one slice of whole-grain bread daily. This 12-week period, called the induction phase, is most important for achieving remission. The third six-week period, the maintenance phase, adds back more foods to make the diet more sustainable.

Even with those adjustments, the diet may be a challenge to adhere to in the long term, and requires in-depth planning plus home cooking, says Henit Yanai, MD, head of the IBD Center at the Rabin Medical Center in Petah Tikva, Israel.

Specific Carbohydrate Diet

The specific carbohydrate diet, which is a grain-free elimination diet, is based on the idea that consuming certain complex carbs feeds unhealthy bacteria, causing an overgrowth of these "bad" bacteria in the small intestine. That in turn could contribute to inflammation. The diet cuts out everything from table sugar to grains—including wheat and corn—starchy foods like potatoes, and other exclusions. Adherents can, however, have meats, fish, and poultry without additives, veggies (fresh or frozen, but not canned with any additives), and most nuts and oils. They can also use honey as a sweetener. However, experts express concern about patients' ability to sustain the diet and advise that such an eating plan should be monitored by a dietitian.

Mediterranean Diet

The Mediterranean diet is another approach recommended to some IBD patients. It's been well studied and is highly touted for its overall benefits, including for heart and brain health. Best of all, it's an eating style recommended for nearly everyone and is easier to follow than more restrictive diets. If you follow this plan, you'll load up on fruits and vegeta-

bles, whole grains, nuts, and lean protein such as fish.

The Mediterranean diet was featured in a rare and prominent head-to-head comparison of diets for IBD, led by Lewis, called the DINE-CD trial. The study, which was published in May 2021 in the journal *Gastroenterology,* pitted it against the specific carbohydrate diet. More than 190 patients with mild to moderate Crohn's were involved in the research.

The study found that both diets similarly helped patients achieve symptomatic remission and improved their quality of life. Neither option had a significant impact on a biomarker used to measure inflammation, something the Crohn's disease exclusion diet has been documented to help improve.

Low-FODMAP Diet

Patients whose Crohn's disease is well controlled in regard to inflammation but who are still suffering from irritable bowel symptoms may benefit from the low-FODMAP diet. (That stands for fermentable oligo-, di-, monosaccharides, and -polyols.)

Primarily promoted for helping to treat IBS, this diet aims to exclude short-chain carbohydrates, or sugars, that are poorly absorbed by the small intestine. Foods that are restricted or avoided on the low-FODMAP diet initially include wheat, dairy, certain fruits, such as apples, and veggies such as artichokes and asparagus.

"If people have significant pain and bloating and nothing else is working, then perhaps I might suggest that they try the FODMAP elimination diet," says Jean Fox, MD, a gastroenterologist at Mayo Clinic in Rochester, Minnesota. But she says that she generally has her patients follow the approach under the supervision of a dietitian, so they don't continue the restrictive phase for more than six weeks. ☐

HOW TO SLEEP BETTER

An inflamed digestive system and insomnia can be common bedfellows. Certain therapies can help people sleep better and provide relief.

BY MARKHAM HEID

A LOT OF PEOPLE WITH INFLAMMATORY BOWEL disease (IBD) have trouble sleeping. By some estimates, roughly 75 percent of people with IBD experience sleep disturbances such as trouble falling asleep, trouble staying asleep, and poor overall sleep quality. Meanwhile, surveys of IBD patients have found that poor sleep tends to be the top contributor to quality-of-life issues.

The fact that so many people with IBD experience problems sleeping is bad news for a number of reasons. For one thing, a lot seems to go wrong with the human mind and body when sleep is inadequate; sleep disorders such as insomnia are strongly linked to an increased risk for a range of mental and physical health conditions, including depression and Alzheimer's disease. But second, and maybe more important, researchers have found that poor sleep may worsen pain, fatigue, and other symptoms among people with inflammatory diseases like IBD.

While the relationship between poor sleep and IBD is something experts are still working out, they've already found evidence that the two conditions may have a bidirectional relationship, meaning they contribute to one another in unhelpful ways. According to the authors of a 2020 study in the journal *Crohn's & Colitis 360*, people with IBD who sleep poorly may slip into "a cycle wherein sleep disturbance and IBD worsen and maintain one another, deteriorating quality of life and worsening overall disease activity and inflammation." Another 2020 study, this one in the journal *Inflammatory Bowel Disease*, found that poor sleep was associated with greater inflammation and greater overall disease activity in people with IBD.

"In the clinic, I see a lot of IBD patients who wake up during the night due to symptoms," says Faten Aberra, MD, a gastroenterologist and associate professor of medicine at the Hospital of the University of Pennsylvania. But that's only one way sleep and IBD may be interrelated. Depression is common among people with IBD, and it's strongly linked to insomnia. Plus, some IBD medications can cause sleep

disturbances. Determining how best to help an IBD patient manage their sleep problems depends in part on these and other underlying drivers.

The good news is that medical science is getting better at recognizing and treating the sorts of sleep issues that afflict people with IBD. Here, experts discuss the relationship between these two medical conditions, as well as how best to manage IBD-related sleep disturbances.

IBD and Sleep

Sleep has a profound effect on the immune system. Researchers have found that levels of several cytokines—which are proteins that orchestrate the immune system's inflammatory processes—tend to shift in predictable ways after a bad night's sleep. In simple terms, the immune system often reacts to poor sleep as though it has encountered some kind of physical threat: It ramps up its defenses, including its levels of inflammation-stoking cytokines.

"We discovered some time ago that sleep loss produces a marked activation of inflammation at the cellular level," says Michael Irwin, MD, a professor of psychiatry and biobehavioral sciences at the David Geffen School of Medicine at UCLA. Sleep disturbances also shift the regulation of genes that play a role in immune functioning, he says: "We know that in people who have underlying autoinflammatory diseases such as rheumatoid arthritis, inflammation and pain go higher when they're deprived of sleep." Research has found similar effects among people with IBD. Poor sleep is associated with an increased risk for flares among people with both ulcerative colitis and Crohn's disease. And in people whose IBD is not well controlled, poor sleep seems to make symptoms worse.

While a night of poor sleep seems to heighten the severity of IBD, it's also true that IBD interferes with sleep. "Inflammation is a biological signal that impairs depth of sleep," Irwin says. "So you can get into this spiral of sleep disturbances and inflammation contributing to each other."

Meanwhile, some mental or physical health problems that often co-occur with IBD can also contribute to sleep problems. For example, psychological disorders seem to be a common cause of IBD-related sleep disturbances. "When we look at the things that people say are most impactful for their sleep, it's not just the usual suspects—so not just bowel movements at night or abdominal pain," says Jessica Salwen-Deremer, PhD, psychologist and sleep specialist at Dartmouth Health who works with IBD patients. "It's more likely to be a general feeling of unwellness, or feeling anxiety about bowel movements."

In support of this, researchers have found that people with inactive IBD are almost as likely as those with active IBD to experience sleep problems. They attribute this in part to the elevated rates of mental-health disorders among IBD patients. "The heightened frequency of depression and anxiety is one explanation for the sleep problems we see," says David Sachar, MD, an IBD specialist and professor of medicine at the Mount Sinai School of Medicine in New York City. By some estimates, roughly 1 in 5 people with IBD has an anxiety disorder, and the incidence of depression among people with IBD is only slightly lower. A much higher percentage of IBD patients experience symptoms of anxiety and depression, and both of these mental-health problems tend to cause sleep disturbances.

Finally, Sachar says that IBD medications can mess with a person's slumber. "People with IBD are often on steroids, and those can interfere greatly with sleep," he says. Other medical conditions, including sleep apnea, are also major causes of sleep disturbances.

It's easy to see why experts so often describe the relationship between IBD and sleep issues as complex. There's a lot of cross talk between the two conditions, and they may make each other worse. The good news is that by improving one or both sides of the sleep-IBD equation, you may find some relief from both. "You can target sleep and improve inflammation and pain," Irwin says. "And the potency and efficacy of the sleep treatments we have is really remarkable."

Addressing the Problem

When you consider all of the ways sleep and IBD interact, determining how best to remedy the situation can be tricky. Switching up your medications won't help if your sleep issues are caused by sleep apnea or depression. Likewise, going to a sleep specialist for insomnia treatment won't do you much good if you're up at night due to your medications or uncontrolled IBD symptoms.

Determining the source (or sources) of your sleeping problems can involve some trial and error, but it's best to start by talking with your IBD care provider. They're used to hearing about sleep disturbances

from their patients, and they can help you narrow down the likely causes and best remedies. That's true even if your sleep problems aren't directly caused by your IBD. For example, Aberra says that when her patients mention they're having problems sleeping, she often recommends depression screening because she knows this is a common underlying issue and a cause of insomnia.

Sachar adds that, in his experience, people with IBD often have a good idea about what's causing their sleeping problems. "They tend to know if it's due to psychic effects, medication effects, or because of symptoms like having to get up and go to the bathroom," he says. Don't be afraid to tell your care team what you think is going on. A change in medications, or the addition of new meds to treat uncontrolled symptoms, could help you sleep more soundly, he says.

On the other hand, experts say that sleeping pills may not be the best solution. For one thing, these medications may not mix well with the drugs you're taking to manage your IBD symptoms. There are also non-drug sleep remedies that may provide more durable relief from insomnia and all of its related harms.

Arguably the most efficacious and evidence-backed sleep treatment is cognitive behavioral therapy for insomnia, or CBT-I. Some early research has found that CBT-I not only helps people sleep better, but may reduce IBD-related issues such as chronic pain, depression, and inflammation. "In our initial pilot trial among people with mild to moderate IBD, we saw some really awesome sleep outcomes," says Salwen-Deremer. "People had quite significant reductions in the time it took to fall asleep and time awake during the night, and also increases in the duration of sleep." People also reported reductions in disease activity, she says.

What is CBT-I? Salwen-Deremer says it's a multicomponent treatment that includes education in proper sleep hygiene and stimulus control. (This is stuff most of us have heard about, like sticking with a consistent sleep-wake schedule, and avoiding caffeine, exercise, or other stimulating activities in the evening or before bed.)

But there's a lot more to CBT-I than that. "It also involves sleep restriction, which is not something most people have experience with," she says. In a nutshell, sleep restriction entails temporarily cutting down the time you spend in bed each night in order to deepen your sleep and improve your "sleep efficiency," which is the proportion of your time in bed that you actually spend asleep.

Salwen-Deremer says CBT-I also involves relaxation training, as well as cognitive therapy. "This is where we examine how your thoughts may set you up for arousal in bed, and how to dispute those thoughts and create new balanced thought patterns that support sleep," she explains.

While CBT-I may be effective for some forms of IBD-related insomnia, it's not appropriate for all patients. For example, if you're in the midst of a bad flare, sleep restriction isn't a good idea, she says. Also, CBT-I won't do you as much good if your sleep problems are caused by sleep apnea or your IBD medications.

BY IMPROVING ONE OR BOTH SIDES OF THE SLEEP-IBD EQUATION, YOU MAY FIND SOME RELIEF FROM BOTH.

If you and your care provider determine that CBT-I may be helpful, she says it's best done with the help of a trained professional. Digital resources or apps—Salwen-Deremer mentions Insomnia Coach and Sleepio as two evidence-backed options—are also helpful if you want to give CBT-I a try.

A Complicated Puzzle

The relationship between sleep and inflammatory bowel disease is complex. There's a lot of evidence that the two are interrelated, but researchers are still sorting out precisely how they play together—and how treating one may help relieve the other.

While more work is needed, experts are beginning to nail down the most effective remedies. Already they've found that changing up your medications, addressing underlying psychological and medical issues (such as depression or sleep apnea), and improving your sleep with the help of therapies like CBT-I may all be useful. The bottom line is that if you have IBD and you're not sleeping well, you don't have to live with it. There are solutions. ☐

MANAGING IBD

NEW FRONTIERS FOR INFUSION THERAPIES

Intravenous infusion therapies have long been expensive and inconvenient. Experts examine the latest developments and the urgent need for new remedies.

BY MARKHAM HEID

THE HUMAN GASTROINTESTINAL TRACT CAN BE a hostile place for visitors. It's filled with digestive acids and microorganisms that rapidly break down swallowed bits of food, and it can be just as rough on non-food molecules. That includes some of the latest drugs for the treatment of inflammatory bowel disease (IBD).

"Some medications that target the immune system don't work if they're swallowed because your gut would digest them like a piece of steak," says Gilaad Kaplan, MD, a gastroenterologist, IBD researcher, and professor of medicine at the University of Calgary. "You have to deliver these medications to the immune system in a way that bypasses the GI tract." One method of bypassing the gut is known as an infusion, which is essentially a drawn-out intravenous injection.

Infusion therapies for IBD have long been used in patients who need rapid, high doses of a drug, or who are too unwell to swallow pills. For example, Kaplan says, people with IBD who are very sick and hospitalized are sometimes administered systemic corticosteroids via intravenous infusion. However, infusions have become a more common method of delivering IBD drugs thanks to the emergence of biologics. Biologics are medicines made from living cells that are designed to locate and alter the activity of immune system proteins that promote inflammation, and many of them have to be administered via infusion.

"Traditional chemical drugs bind to receptors on cells, which can lead to a whole cascade of things happening on a cellular level," Kaplan explains. While this cascade can be helpful, it can also give rise to negative side effects. "The cool thing about biologics is that they usually only block a single protein," he says. As a result, these drugs are often capable of altering immune functioning or inflammation very narrowly. Put another way, the medication's effects are often more targeted and less likely to result in unwanted side effects, he says.

Many types of IBD therapy involve needle injections. But infusions aren't the same as a simple

shot. "There are some subcutaneous shots that the patient can administer themselves at home," says Bruce Sands, MD, chief of the division of gastroenterology and a professor of medicine at the Icahn School of Medicine at Mount Sinai. "With an infusion, the drug is usually diluted with something like salt water and given in greater volume via an intravenous catheter." The infusion can last anywhere from 30 minutes to a couple of hours, he says, and therefore self-administration is not an option. Most people have to visit a hospital or clinic to receive the treatment, which can be time-consuming and inconvenient—especially for those who don't live near a medical facility.

On the other hand, while most oral drugs (and some injectable treatments) are taken on a daily basis, infusion therapies are usually more spread out. "The biological half-life of infused drugs tends to be much longer than an oral pill," Kaplan says. This means it takes the human body more time to clear out the drug, and so the therapeutic effect of an infusion therapy can last for weeks or even months, as opposed to mere hours for an oral drug.

After the initial "loading doses" of a biologic infusion therapy are completed—something that can take six to 12 weeks—later maintenance doses tend to be required only once every two months. "The relative infrequency can be a benefit," Sands says. Also, because these therapies are administered in a medical setting, nurses or other providers are on hand to monitor and address potential adverse reactions. "These are very rare, but they might include things like shortness of breath or a rash, or a sudden drop in blood pressure," Sands says.

Like most other IBD treatments, infusion therapies are usually taken indefinitely. "These drugs are not cures—they only suppress the immune or inflammatory state," Sands says. "Patients usually relapse if we stop the treatment." Infusion therapies also tend to be expensive. Annual costs of biologics, for example, run between $20,000 and $30,000, and insurance usually covers the tab only for people with severe IBD who haven't responded well to less-expensive treatments.

LIKE MOST OTHER IBD TREATMENTS, INFUSION THERAPIES ARE USUALLY TAKEN INDEFINITELY.

The Newest Infusion Therapies

Infusions of biologics have been a mainstay of treatment for moderate and severe IBD for the past 20 years. But a lot has changed during those two decades—and especially during the past seven years. "We've been using infliximab since the early 2000s, and in 2005 adalimumab came along," Kaplan says. Both of these biologics began as treatments for other immune disorders but were eventually shown to benefit people with IBD. Both work by interfering with an immune system molecule called tumor necrosis factor, or TNF. "TNF is basically a messenger molecule that calls on an inflammatory response," Kaplan explains. "With Crohn's disease and ulcerative colitis and other immune diseases, TNF is perpetually being expressed and telling the immune system to effectively attack 'ghost' pathogens that aren't really there." Infusions of TNF blockers can stop those inappropriate attacks by binding to TNF receptors, which limits the molecule's ability to stoke inflammation.

While anti-TNF infusion therapies are effective, they can in some cases impair the immune system's ability to fend off infections. These drugs are also associated with a small increase in risk for blood malignancies such as lymphoma, Kaplan says. TNF blockers are still used today (they can be especially useful for people who have IBD and other common immune conditions, such as rheumatoid arthritis), but the latest infusion therapies are more targeted and less likely to cause side effects. "The immune system is like a tree with all these branches coming out of it," Kaplan says. "We really want to prune the branches that are causing the problems while leaving the rest of the tree alone." Some of the newest biologics accomplish this by manipulating the activity of immune system molecules known as integrins. These diverse molecules are akin to small branches on the outskirts of the immune-system tree. Turning them off leaves most of the immune system intact. "They're targeting a very finite area while leaving the rest of this complex network alone, which has been a huge breakthrough," Kaplan says. For example, ve-

dolizumab is an anti-integrin infusion therapy that selectively blocks the immune response in the gut and is used in the treatment of IBD.

In medical science, new advancements often reveal new challenges, and that has proved true for the development of IBD infusions. "As we're doing more immune-system analyses, what we're finding is that different IBD patients have different cytokine profiles," says Karen Madsen, PhD, an IBD researcher and professor in the division of gastroenterology at the University of Alberta. "We're learning that no matter how good the drug is, only a subset of patients will actively respond."

Even if a person does respond well to a drug, there's no assurance that this response will continue indefinitely. "Another thing we've learned is that this disease has escape mechanisms," Kaplan says. "It finds ways to bypass the immune system, and so we sometimes need to use another drug to recover the good response." Biologic infusion therapies are sometimes combined with oral medications. "The immune system is so complex that sometimes blocking one of these proteins is not enough," he explains.

Who Is a Good Candidate?

Answering that question is tricky. Experts say that no two IBD patients are the same. Medical science is getting much better at identifying immune system markers, or biological indicators, that can predict a person's response to an infusion therapy. Even then, it can still be difficult to predict how well a person with IBD will react to an infusion therapy. "Right now, these are usually reserved for people with moderate-to-severe disease who are not doing well on other treatments," Kaplan says. "We usually don't start with biologic infusion therapies; we escalate up to them."

Because of the high cost and logistical burden of administering infusion therapies, many people who might benefit aren't on them. "It's safe to say that a higher proportion of patients are good candidates than are actually getting them," Sands says. When it comes to biologics, he says that—for reasons that are unclear—people with Crohn's are more likely to receive these drugs than people with ulcerative colitis. "We see more widespread use in Crohn's," he says. "Estimates are that somewhere around 30 percent of people with Crohn's may be getting a biologic therapy, and it's maybe 15 or 20 percent in people with ulcerative colitis." Sands and other IBD experts agree that these drugs have been truly revolutionary. But like all medications, they come with side effects. Again, these are more commonplace among the older anti-TNF drugs, which can raise a person's risks for skin symptoms (rashes, mostly), infections, and some blood cancers. Sands says the newer biologic medications have a much improved safety profile.

BECAUSE OF THE HIGH COST OF INFUSION THERAPIES, MANY PEOPLE WHO MIGHT BENEFIT AREN'T ON THEM.

Future Therapies

There are efforts to help move these treatments out of the clinic. Recent advances in the equipment and techniques required to administer these drugs have made at-home use possible for some patients. Down the road, many people who need these drugs may be able to take them outside of a medical setting. Meanwhile, the number of effective IBD infusion therapies is growing quickly. "Since around 2015, we've seen an explosion of different biologics working on different mechanisms of action, and I think in the next year or two we'll see a bunch of new therapies for IBD coming to market," Kaplan says.

The need for newer and more convenient IBD drugs is urgent. For reasons that aren't well understood, IBD is increasingly common across much of the world. It's also becoming more prevalent in younger people. Kaplan says that changes in the composition of the gut microbiome—the community of organisms that resides in the human GI tract—are likely a major contributor to the rising prevalence of IBD. But there's no simple answer to the question of what's going wrong with our gut. A mix of inherited and environmental factors is likely at play. While experts are sorting that out, the latest infusion therapies are providing durable relief for people with IBD. "Our ability to treat these conditions has really improved," Kaplan says. ◻

3

FEEL BETTER EVERY DAY

Simple lifestyle changes can stave off chronic inflammation, helping to foster a healthier and happier life.

HOW STRESS MAKES US SICK

Prolonged psychological stress can lead to an inflammatory response that harms the body and the mind. Here's how to manage the response.

BY CAROLYN WILLIAMS, PHD, RDN

EXTERNAL CAUSES OF STRESS ARE PREVALENT IN today's world. Political divides, extreme environmental events, economic uncertainty—and all of it intensified by nonstop news access and social media pressures. The stress level of Americans, studies show, has been increasing over the past few years.

As a result, many people find themselves struggling with decreased productivity, low energy, lack of focus, disrupted sleep, and less consistency in health habits related to diet and exercise, all side effects that are frustrating and not conducive to long-term wellness. However, it's a more subtle effect—low-grade inflammation—that research suggests is the real cause for concern when it comes to ongoing stress. Generated and exacerbated by stress, inflammation is linked to an increased risk for a multitude of conditions including heart disease, diabetes, autoimmune conditions, depression, and Alzheimer's, as well as an increased rate of aging.

Here's some good news, though: Not all stress is inflammatory and harmful to health. Some stressors can even be positive or motivating. Also, the body has a built-in mechanism to respond to stress. So in order to understand the stress-inflammation connection and how to minimize its effects, it's important to first find out more about stress and how the body responds to it.

What's Got You Stressed?

Stress is caused by stressors, events or situations that an individual perceives to be a threat or challenge. Stressors can be psychological, like pending deadlines, a big exam, financial worries, a major life change such as a death or divorce, or conflict with others, or they can be physical. Some physical stressors are from the environment, such as pollution, noise, or extreme temperatures, while other physical stressors are related to body conditions, such as lack of sleep, chronic pain, or poor diet choices. How one perceives a stressor determines whether it leads

to good stress (eustress) or bad stress. For example, an upcoming deadline or athletic competition you perceive as challenging yet positive can motivate you and even improve performance. When viewed in a negative light, though, this same stressor can lead to psychological stress, characterized by feelings of worry, pressure, or emotional anguish.

The Body's Response to Stress

When the body encounters a stressor that it deems to be a threat or challenge, the nervous system reacts almost instantaneously. "Our nervous system is wired to force our bodies to react to a threat. This is the traditional fight-or-flight you hear about," explains Tasneem Bhatia, MD (more commonly known as "Dr. Taz" to her followers), an Atlanta-based integrative medicine physician and author of *The Hormone Shift*. The fight- or-flight response triggers the release of the hormones adrenaline and cortisol that trigger immediate effects to enable the body to outrun, fight, or overcome the threat. Adrenaline speeds up heart rate, breathing, and reaction time, while cortisol increases available glucose in the bloodstream to use for quick fuel.

Once the stressor is under control or gone, the stress response slowly dissipates as adrenaline and cortisol levels decline, allowing heart rate and breathing to slow, muscles to relax, and the body to return to a state of homeostasis. The fight-or-flight response is designed to promote survival of the human species, and, according to Bhatia, we wouldn't be able to react to threats in a timely manner if this didn't happen. The response is engineered to be a good thing, even lifesaving at times. But it's also designed to be a short-term, temporary response, not a long-term or ongoing one.

How a Good Thing Goes Wrong

Health problems arise when the stressor—and consequently, the stress response—sticks around. Another layer to this problem is that most of today's top stressors are ongoing or long term. This is in contrast to prehistoric times, when the stress response was largely needed to survive physical dangers (such as outrunning a tiger) that had a clear start and end. Today, there tend to be fewer physical stressors and more long-term psychological ones without a clear or definite end. Bhatia cites the juggle of work, family responsibilities, and finances (and their ongoing nature) as some of the top stressors she sees in her practice: "We are all overly connected now, so there are no natural breaks like we once had." Stanford University School of Medicine professor Greg Hammer, MD, has similar thoughts, calling many of today's stressors "monumental," such as the residual effects of the pandemic, financial hardship, social isolation, the political divide in the U.S., global warming, and even worry about what the world will look like for our grandchildren and great-grandchildren.

When the stress response is prolonged, the body stays in a state of fight-or-flight, and hormones remain elevated. The increases in these hormones are beneficial in the short term but can later lead to health issues. According to Hammer, "Over a long period of time, they become maladaptive. The increase in heart rate and blood pressure produced by adrenaline causes a strain on the heart, increasing its need for blood and oxygen flow and potentially leading to a heart attack." He adds that chronically elevated cortisol levels due to stress

A relaxing walk can ease low-grade inflammation and help with stress management.

may predispose a person to diabetes. This is because elevated cortisol levels increase blood glucose and slow insulin production. Initially, this is good, because it provides the body fuel to get away from a pending threat. But over time, elevated cortisol levels contribute to hormone imbalances, weight gain, and the development of atherosclerosis and heart disease.

The Stress-Inflammation Connection

While the simple physical or mental burden of a stressor can trigger low-grade inflammation, the connection between stress and inflammation goes deeper. This is because the immune system is intricately connected to the nervous and endocrine systems. In fact, the three systems are dependent on one another, each relying on feedback from the others to maintain homeostasis and function properly. This means an issue or problem in one system will impact the other two. In the case of long-term or ongoing stress, an overstimulated nervous system and an endocrine system with hormonal imbalances will lead to an immune system that is less effective at protecting the body and that generates low-grade inflammation. "Together, chronic stress and low-grade inflammation induce or exacerbate a variety of life-threatening health conditions, including neurodegenerative disorders such as Alzheimer's disease, depression, cancer, and cardiovascular disease. Inflammation also contributes to cellular aging, which could make our biologic age greater than our chronologic age," Hammer says.

Short- and Long-Term Effects of Stress

The physical impact of stress depends on its severity and length. Immediate symptoms that people often experience are disruptions to normal GI habits and changes to one's usual sleep habits. As the stress response sticks around, Bhatia says, it is common to experience fatigue, increased anxiety, weight loss or gain, altered menstrual cycles, acne, hair loss, changes in mood, and an increase in sugar or salt cravings. Due to suppression of the immune system, many people may also find themselves more susceptible to illnesses such as colds or flu. If the stress response continues, Bhatia says, cortisol levels will crash at a certain point, leading to exhaustion and burnout and more severe symptoms.

Hammer says he commonly sees changes occur in key health habits—specifically sleep, exercise, and diet—as a result of stress, which can further aggravate existing symptoms, hormonal imbalances, and inflammation. "Stress impairs our sleep, causing fatigue. Fatigue undermines our commitment to regular exercise, which is crucial to our health in many ways. When we are tired and experience low energy levels, we tend to pick up sugary and fatty so-called 'comfort foods,' which may give us a temporary boost but are deleterious to our health. Poor diet and lack of exercise compromise our sleep, and the cycle becomes self-perpetuating. These factors, in addition to the direct effects of stress on our bodies, can result in hypertension, diabetes, cardiovascular disease, poor immune function and cancer risk, and neurodegenerative disease," he says.

The Toll on Mental Health

The damage caused by ongoing stress and low-grade inflammation isn't limited to physical health. Research suggests it may also impact a person's mental health and long-term brain health. Over a decade ago, researchers noted that individuals diagnosed with depression had significantly higher levels of inflammatory blood markers. Today, neuroinflammation (low-grade inflammation in the brain) is considered is a major player in the development of depression and anxiety, and a top cause of neuroinflammation is prolonged stress.

The hormones and inflammation associated with the stress response appear to alter the structure and functioning of the hippocampus and other areas of the brain that increase risk for the development or progression of depression and anxiety, and may aggravate other conditions affecting mental wellness, such as ADHD, PTSD, and schizophrenia.

Chronic stress also seems to play a role in advancing normal cognitive changes associated with the natural aging process to more significant dementia, including neurodegenerative diseases such as Alzheimer's disease. Many factors play into Alzheimer's development, one of which may be changes in the brain induced by the stress response. Once the disease is in development, the stress of Alzheimer's on the brain may influence its progression. As a noted Alzheimer's researcher explained, "stress causes disease, and then disease causes stress," creating a self-perpetuating cycle of stress and inflammation.

Journaling about your thoughts and fears is a highly effective tool for stress relief.

Minimizing Stress

Stress is inescapable in today's world, and how we respond and manage that stress can significantly influence its impact on our physical and mental health. Finding and adopting a few daily or weekly habits to help lower your stress levels is key when you're going through challenging periods. Regularly practicing habits that calm the body and mind can not only minimize inflammatory and health effects of stress but can also help build your resilience when it comes to future stressors. Resilience refers to the body's ability to adapt to challenges, and building resilience enables a person to deal with stress more effectively, minimizing its impact on health when it does come up.

Most any form of gentle movement, meditation, conscious breathing, or quiet time spent doing things such as journaling can be effective. If you need an idea to get started, Bhatia suggests taking a "20-minute time out" each day. This could mean starting your morning with 20 minutes of exercise or meditation, taking a midday walk, or ending the day with a session of prayer or journaling.

Need something quicker? Hammer advocates a mere three minutes of mindful breathing. "Taking in a prolonged breath through the nose, pausing, and then exhaling slowly activates the parasympathetic nervous system," he explains. "This slows the heart rate and lowers blood pressure and blood sugar, 'de-stressing' the body and mind." He also points out that simply focusing on gratitude can rewire your brain in a positive way when you're feeling stressed. ◻

Having Lots of Feelings Is Good for Your Health

A brighter outlook has long been linked to a healthier body, but research is finding that all emotions can help calm inflammation.

BY AMANDA MACMILLAN

Happiness isn't the only emotion that can help you stay healthy as you age. How excited, amused, proud, strong, and cheerful you feel on a regular basis matters, too. According to research, people who experienced the widest range of positive emotions had the lowest levels of inflammation throughout their body. Lower inflammation may translate to a reduced risk of diseases including diabetes and heart disease.

Research has long shown that positive emotions may have an anti-inflammatory effect on the body, and the 2017 study, published in the journal *Emotion,* looks at whether the range and variety of those feelings play a role as well. Evolution suggests that they would. Drawing on the evolutionary advantages of ecosystems with plenty of biodiversity, researchers from the United States and Germany wondered if similar perks might exist for variety within the human emotional experience. Such a range may improve physical and mental health by "preventing an overabundance or prolonging of any one emotion from dominating an individual's emotional life," the researchers wrote.

The researchers asked 175 middle-aged adults to keep a daily log of their emotional experiences for a month by recording how often and how strongly they experienced each of 32 different emotions: 16 positive (like being enthusiastic, interested, and at ease) and 16 negative (such as being scared, upset, jittery, and tired). Six months later, scientists tested their blood for markers of systemic inflammation, a known risk factor for many chronic health conditions and for early death.

Overall, people who reported a wide range of positive emotions on a day-to-day basis had less inflammation than those who reported a smaller range—even if their overall frequency of positive emotions was similar. That was true even after researchers controlled for traits like extraversion and neuroticism, body mass index, medication use, medical conditions, and demographics. (A similar effect was *not* observed for the other end of the spectrum: Whether people regularly experienced many or only a few variations of negative emotions didn't seem to affect their level of inflammation.)

Lead author Anthony Ong, PhD, professor of human development at Cornell University, suspects that people may be able to maximize these benefits by more closely examining their emotions. "When it comes to infusing more diverse positive emotions into our lives, it may turn out to be a simple daily practice of labeling and categorizing positive emotions in discrete terms," he says. "Pay attention to your emotions and learn how to better mentally recognize situations that, for example, make you feel calm versus excited."

Ong acknowledges that there may be unforeseen reasons why people with a smaller range of positive emotions may have higher inflammation. "It could also be that people with higher inflammation for some reason may be the ones who tend to report lower levels of positive emotional diversity," Ong suggests. More research is needed, but this study strengthens the link between many kinds of happiness and better overall health. ☐

FOODS TO TAME INFLAMMATION

These healthy foods are loaded with antioxidants that can protect the body from inflammation.

BY ALEXANDRA SIFFERLIN

INFLAMMATION IS THE BODY'S HEALTHY RESPONSE to fighting disease. But when it gets out of control, inflammation can become chronic and lead to a whole host of health problems, from autoimmune diseases to cancer. Foods high in sugar and saturated fat are thought to contribute to inflammation, which is why some people who have inflammatory conditions and autoimmune disorders try low-sugar diets. On the other hand, some foods may actively tamp down inflammation. Here are some of the most effective.

Bell Peppers

Bell peppers—especially the bright-red ones—are high in antioxidants and low in starch. Both spicy peppers and sweet bell peppers contain the chemical compound capsaicin, which is known to help reduce inflammation and potentially even pain. Chop up bell peppers and serve them with hummus or drizzled with a little red-wine vinegar, salt, and pepper.

Spinach

With its reputation as a power food, spinach is a good source of vitamin E, which may help protect the body from inflammation-causing molecules called cytokines. The dark color lets you know that it is nutrient-dense, like other leafy greens. Make a spinach salad with a high-fat food like avocado in order to take full advantage of the veggie's nutrients.

Black Tea

Green tea usually gets the attention, but black tea (which comes from the same plant) also has benefits. Drinking black tea may help keep arteries open, and it contains antioxidants that are known to protect cells from damage. One study linked black tea to a substantially lower risk of ovarian cancer. Black tea tastes great on its own or with a bit of milk and honey, or you can add some lemon and pomegranate juice for a refreshing iced beverage.

Buckwheat

Eating grains may reduce blood levels of a marker for inflammation called C-reactive protein. Buckwheat (shown above) is also gluten-free, making it a safe option for people with celiac disease (double-check the label, though). Buckwheat is used to make soba noodles, which you can get in grocery stores and use in soups. You can also buy the grain on its own and use it in place of rice.

Mackerel

The fat in fish such as mackerel helps fight several diseases that are characterized by high inflammation, such as heart disease and Alzheimer's. Mackerel is also a good source of vitamins B_{12} and D, the latter of which can be hard to find naturally in foods. Vitamin D is important for maintaining strong bones and immune-system function, as well as helping the body to better absorb calcium. Mackerel is a staple of the Mediterranean eating plan. Roast a fillet (or the whole fish if you're adventurous) with a generous helping of herbs, olive oil, and lemon and enjoy.

Garlic

The scent of garlic tips you off to its many health benefits. The pungent aroma comes from sulfur compounds, including allicin. Scientists believe that allicin may block enzymes involved in infe tions, and some studies suggest that swallowing garlic may ward off colds. (It's probably easiest to eat garlic cooked with other foods, although some peo-ple can stomach eating a bit raw, followed by milk or water.) Research has also linked garlic intake to a lower risk of stomach, colon, and esoph gus cancers. For a flavor and immunity boost, add some garlic to marinades, roasted vegetables, or grain bowls.

Jalapeño Peppers

Jalapeños get their spice from a compound called capsaicin, which is something of an all-star in the nutrition world. Capsaicin acts as an anti-inflammatory agent and may ease arthritis symptoms. Some research suggests it can also keep your metabolism humming. Add diced jalapeño peppers to guacamole for an extra kick of flavor. You can also mix these peppers into your favorite cornbread recipe.

Pomegranate Seeds

A good source of antioxidants, pomegranate seeds can lower both cholesterol and blood pressure. Experts think that a compound they contain called punicalagin targets inflammation in the brain, which could help slow the progression of brain-related decline. Many grocery stores now sell prepackaged pomegranate seeds, but if you'd rather purchase the full fruit, just cut it in half and spoon the seeds into a bowl to munch on, or add them over yogurt or to a salad.

Apples

People who eat their apple a day use fewer prescri tion medications, according to a 2015 study. And regular apple eaters report fewer asthma symptoms, according to British research—they contain a flavonoid called khellin that may open up airways. Apples are also high in fiber, which can help reduce the inflammation common during infections. Bonus: They're a superfood when it comes to satiety. To turn apples into a more energizing snack, slice one up and enjoy it with a spoonful of peanut or almond butter. Buy organic, or wash well before eating: A recent study found that a little water and baking soda removes pesticide residue.

Chamomile

Dried chamomile flowers have been used for hudreds of years, and there's some research suggesing that the tea helps an upset stomach. The flowers contain compounds called flavonoids that may help reduce inflammation and pain. Make a healthy "hot toddy" with hot chamomile tea, honey, and sliced lemon.

Berries

Loaded with healthy antioxidants including anthocyanins, ellagic acid, and resveratrol, berries of all kinds are powerful tamers of inflammation. Anthocyanins, which give the fruits their beautiful deep color, have been shown to have anti-inflammatory properties. You can add these small superfoods to your morning bowl of cereal, or just eat them by the handful—they're delicious fresh, frozen, and dried.

Pears

If you're concerned about inflammation (say, if you have arthritis or diabetes), eating high-fiber foods like pears is a natural way to fight the problem. A fiber-rich diet contributes to a healthy microbiome and promotes satiety—helpful when trying to lose weight. Slice up pears and add them to a salad with walnuts and a soft cheese.

Olive Oil

Research has found that the antioxidant oleocanthal, which is found in olive oil, has a similar effect as ibuprofen, a common anti-inflammatory drug. You can substitute olive oil in recipes that require canola oil or butter, dip your bread in olive oil, or use it as a salad dressing. Just be sure you are using extra virgin olive oil, which is made from pure cold-pressed olives rather than a blend of processed oils.

Ginger

Ginger, which is sometimes recommended to treat nausea, is high in both antioxidants and anti-inflammatory properties. A recent review of 60 studies found that ginger might have beneficial effects on ailments such as obesity, heart disease, and diabetes. It also contains immune-system-supporting compounds such as beta-carotene and capsaicin. Toss freshly ground ginger into a tofu stir-fry, or sip it in tea.

Honey

Honey is high in antioxidants, which have important anti-inflammatory properties. It has also been shown to help soothe sore throats and coughs, as well as stomach irritation. You can make a simple honey glaze to drizzle on everything from nuts to carrots to fish.

Tomatoes

It is a common misconception that nightshade vegetables, such as tomatoes, can aggravate inflammation, but research has shown the opposite to be true. Tomatoes contain vitamin C and antioxidants, which are both anti-inflammatory agents. Try to incorporate them into sauces and salads.

Sage

Sage leaves, which can be made into a tea, are an ancient remedy for sore throats, cough, and colds. One Swiss study found that using sage with other herbs such as echinacea can help relieve throat irritation. Combine sage, goat cheese, and eggs for a flavor-filled omelet. You can also try adding this earthy herb to bean soups and chicken, pork, and beef dishes. ◻

—additional reporting by Ava Erickson

Foods to Avoid

Certain ultra-processed foods can make inflammation worse.

Refined carbohydrates
Foods such as white bread or pasta have had their fiber removed, which means they are missing many of the crucial nutrients that promote digestion and gut health. Refined carbohydrates also have a higher glycemic index (GI), meaning they raise blood sugar faster than low GI foods. Research has found that low GI diets, which consist of unprocessed carbohydrates, can significantly reduce inflammation.

Fried foods
French fries, doughnuts, and onion rings can be inflammatory. The high heat associated with frying increases the production of advanced glycation end products (AGEs) and increases the amount of trans fats in the food, both of which cause significant inflammation in the body.

Sugar-sweetened beverages
Soda and other sugary drinks (like sports drinks, sweet tea, or alcoholic beverages) contain high levels of refined sugar. A 2018 study found that drinking just one soda per day significantly increased levels of the inflammation marker C-RP.

Red and processed meats
Burgers and steaks and processed meat such as hot dogs or deli meat are high in saturated fats, which are key instigators of inflammation. Like fried foods, these meats are often cooked at high heat, which increases the production of AGEs, causing inflammation.

THE CANNABIS REMEDY

Emerging research suggests that medical marijuana can help treat some inflammatory disorders.

BY STACEY COLINO

WHEN JOE SILVERMAN DEVELOPED CROHN'S DISEASE AT AGE 21, the initial symptoms were mild. While the sight of blood in his stool freaked him out, what really bothered him was the frequent abdominal pain and bloating that occurred as his condition progressed to moderate and then severe. Dietary changes didn't make a difference, so he began taking prescription oral anti-inflammatory drugs that are often used to treat certain bowel diseases, which alleviated but didn't eliminate his discomfort. He started using prescription steroid suppositories to cope with flare-ups of the inflammatory bowel disease.

Even so, "I didn't feel well—my mind was cloudy, and I was in pain," says Silverman, co-founder of the PSMC5 Foundation, which is dedicated to beating rare genetic disorders such as the PSMC5 gene mutation (which his son has). So in 2013, he tried a new approach: intravenous infusions of an immunosuppressive drug at four- to eight-week intervals to reduce inflammation in the lining of his intestines. "It helped, but I still had nausea, brain fog, discomfort, and trouble sleeping," Silverman says.

In 2018, he decided to try something different as an adjunctive treatment, with his gastroenterologist's blessing: medical marijuana, in the form of cannabidiol (CBD) and tetrahydrocannabinol

(THC) capsules that he was able to purchase after getting a New York City medical-marijuana license. "Within an hour and a half of taking them, I felt better," he says. "The bloating and pain went down, and my appetite came back."

For centuries, marijuana, which is derived from the plant *Cannabis sativa,* has been used for both medicinal and recreational purposes. On the medicinal front, cannabinoids—a group of compounds that constitute the active ingredients in the marijuana plant—have been found to help alleviate chronic pain, as well as the nausea and vomiting that stem from chemotherapy for cancer. The U.S. Food and Drug Administration (FDA) has even approved specific cannabinoid products for chemotherapy-induced nausea and vomiting in cancer patients and to stimulate appetite in patients with AIDS who have lost weight.

In recent years, there has been growing interest in the use of medical marijuana for gastrointestinal disorders such as inflammatory bowel diseases (IBD) such as Crohn's and ulcerative colitis (UC). In a study published in *Inflammatory Bowel Diseases* in December 2013, researchers surveyed 292 patients with IBD at a major medical center in Boston about their use of marijuana. Twelve percent were active users, and 39 percent were past users. Among those who formerly and currently used marijuana products for their symptoms, the majority felt that it was "very helpful" in relieving abdominal pain, nausea, and diarrhea. More recently, a 2018 study in the *Journal of Pediatrics* found that among 99 teen and young-adult patients with IBD, nearly one-third had used marijuana—and 57 percent of those users endorsed its use for at least one medical reason, most commonly relief of physical pain.

"A lot of people perceive this as a more natural therapy and preferentially want this over immunosuppressants for inflammatory bowel disease," says Byron Vaughn, MD, an associate professor of medicine and co-director of the IBD program at the University of Minnesota. However,

if anything, experts see the primary role for cannabis as an adjunctive therapy, not as a replacement for medications that are used to treat IBD and other gastrointestinal disorders.

Help or Hype?

Research investigating the effects of medical marijuana on various gastrointestinal disorders is limited, so there are many unanswered questions. Right now, one of the obstacles is the federal government's classification of cannabis as a Schedule I drug (along with heroin, LSD, and ecstasy). This reality has inhibited research in the U.S. to evaluate the effects of cannabis on gastrointestinal disorders, as well as other medical conditions.

And while the mechanisms of action aren't completely understood, this much is clear: The human body has an endogenous cannabinoid system—one that originates inside the body—that comprises cannabinoid receptors, endogenous cannabinoids (lipids that engage cannabinoid receptors), and enzymes that are involved in the synthesis and degradation of the endocannabinoids. In particular, CB1 receptors are abundant in the central nervous system, while CB2 receptors are more prevalent throughout the gastrointestinal tract, explains Jami Kinnucan, MD, an assistant professor of medicine in the division of gastroenterology and hepatology at the University of Michigan.

A little background about cannabis: While it contains hundreds of compounds, the most well-known are THC and CBD. THC is responsible for marijuana's psychoactive effects (that "high" sensation), whereas CBD is not psychoactive but seems to modulate the effects of THC, explains Christopher N. Andrews, MD, a clinical professor of gastroenterology at the University of Calgary.

As far as inflammatory gastrointestinal disorders go, the greatest symptom benefit seems to come from preparations that have a combination of THC and CBD, Kinnucan says. This is partly because while CB1 receptors are activated by THC, CBD and THC have a synergistic effect on CB2 receptors. "In patients with inflammatory bowel disease, studies have shown that the combination improves abdominal pain and decreases bowel movement frequency," she says. What's more, cannabis use appears to decrease emptying of the stomach and gastric-acid production, as well as reduce the movement of food throughout the gastrointestinal tract, notes David Poppers, MD, a clinical professor of medicine in the division of gastroenterology and director of GI Quality and Strategic Initiatives at NYU Langone. As a result, cannabis use may improve the diarrhea-predominant form of irritable bowel syndrome (IBS), he says.

Whether cannabis actually improves the underlying causes of GI disorders is less clear. "In the test tube, all cannabinoids have some anti-inflammatory effects," says Jordan Tishler, MD, an instructor of medicine at Harvard Medical School and president of the Association of Cannabinoid Specialists, a professional organization dedicated to education about cannabinoid medicine. "In human studies, if you look for blood markers of inflammation, you don't see any change after using cannabis," he says. When it comes to treating IBD, "there isn't a lot of evidence that cannabis really modifies the underlying disease process. But it treats the symptoms people have."

Other experts agree. "When you tease it out, this

Researchers note that medical marijuana is often used in tandem with other clinical treatments.

is more of a symptom-based therapy," Vaughn says. "With IBD, there seems to be a calming effect on symptoms such as nausea, vomiting, pain, and diarrhea." Vaughn reports that he sees patients with Crohn's disease get more relief from cannabis than those with ulcerative colitis do.

In a review of 20 studies in the *Journal of Clinical Gastroenterology* in 2020, researchers examined cannabis use among patients with IBD and found that cannabinoids had no effect on inflammatory biomarkers, and they were not effective at inducing remission, which is the ideal end point. However, patients who used cannabinoids reported significant improvements in abdominal pain, nausea, diarrhea, appetite, and overall well-being.

Similarly, a double-blind, randomized, placebo-controlled study published in *PLoS One* in 2021 found that patients with mild to moderate ulcerative colitis who smoked marijuana cigarettes daily for eight weeks—while continuing to take their usual UC medications—experienced improvements in their symptoms and quality of life compared with those who were given placebo cigarettes containing cannabis flowers from which THC had been extracted. However, neither group experienced reduced inflammation, based on blood tests.

All that said, it's possible that the impacts of cannabinoids on symptoms could have trickle-down effects that decrease the need for other prescription drugs. For example, a study in the *European Journal of Gastroenterology & Hepatology* in 2019 found that when patients with IBD used medical cannabis to treat their symptoms, their need for other medications was significantly reduced over the course of a year because their symptoms improved.

Potential Drawbacks

A cautionary note: There's a tipping point with using cannabis for GI disorders. "Cannabinoids reduce the tone of the lower esophageal sphincter, which can increase heartburn and reflux symptoms," Kinnucan says. "They also decrease gut motility, causing the

stomach to empty more slowly, which can increase nausea and be problematic for patients with gastroparesis," a disorder that delays the movement of food from the stomach to the small intestine.

Another potential risk: Chronic, daily cannabis use can cause cannabinoid hyperemesis syndrome, which is characterized by recurrent nausea, vomiting, and abdominal pain, Andrews notes. "Some people have many months with cannabinoid hyperemesis. Even if they stop using cannabis, it's possible [their usage] may have induced a permanent change," he says.

In addition, some develop a cannabis-use disorder, a form of dependence that occurs when the brain adapts to ongoing use of the drug. A study in the journal *Drug and Alcohol Review* in 2020 found that approximately 27 percent of lifetime marijuana users develop a cannabis-use disorder, defined as problematic or continued use despite experiencing loss of control, social or medical problems, cravings, tolerance, or withdrawal.

"We don't know what the right dose is where patients can have the positive effects and avoid the negative effects—and not all patients respond the same way to the same dose," Kinnucan says. Plus, cannabis is used in many different ways—as edibles, smoking or vaping, dabbing, oils, or tinctures—and the dosing is different with each route.

"There's little regulation of cannabis, and the THC levels are extremely high now," Andrews says. Thirty years ago, the percentage of THC in typically accessible marijuana was in the single digits, he says, whereas these days THC is often 20 percent or higher. With these higher concentrations, "we have no idea what they will do to the [body's] cannabinoid system long term," Andrews says.

There's also a concern that people with IBD and other gastrointestinal disorders might stop using other treatments that have been approved by the FDA for their condition. "Because they feel better, they may have a false sense that they are better," Kinnucan says. "It's important to continue medical therapy to prevent progression of the disease. We know that medication nonadherence is associated with clinical relapse of IBD and could have implications on future disease outcomes."

Looking ahead, "what we need is to really start doing large, multicenter, randomized, controlled studies to examine the effects on IBD, using specific forms of cannabis at specific doses," Tishler says. Until more is known, the onus is on patients to take precautions. For one thing, if you're interested in trying it, find out what the laws are in your area: While some states have fully legalized marijuana, others allow it only for medical purposes, and still others continue to treat it as fully illegal. You'll also want to find out your employer's policy regarding medical marijuana use, in case there's a chance that you may be drug-tested. "With chronic use, marijuana stays in your system for a long time," Vaughn says.

If you're already using marijuana, whether for medical or recreational reasons, it's important to tell your doctor, regardless of whether it's legalized where you call home.

Wherever you live, "you need to talk to your doctor about whether this is right for you," Vaughn says. "It's good to be open—your doctor is not going to be judgmental." While this may seem like a privacy issue, it's important to realize there could be medical risks. For one thing, cannabis can have potential interactions with other medications, such as warfarin (an anticoagulant), benzodiazepines, and barbiturates, Kinnucan warns. Cannabis use is also more likely to cause problems for certain groups of people, like those who are pregnant or breastfeeding, who have a significant psychiatric disorder, or who have a history of substance abuse, Poppers says.

Finally, remember that experts primarily view cannabis as adjunctive therapy—a potential addition on an as-needed basis—for GI disorders. "This is not a panacea or a miracle drug," Vaughn points out. "For some people, it helps their symptoms, and for some people it doesn't."

While Joe Silverman found that medical marijuana does help to ease his Crohn's disease symptoms, he has prioritized finding the most effective drug to treat the underlying cause of his condition. At the beginning of 2021, he and his doctor shifted the course of his treatment, and he began getting intravenous infusions of a different immunosuppressant drug every six weeks. "It has kept the inflammation [of my Crohn's disease] at bay," Silverman says.

Silverman does still use medical marijuana for flare-ups or on tougher days. "With being able to measure these cannabinoid products by a dosed milligram each time, I still feel in control mentally and physically while reducing the pain in my gut," he says. That's the best of both treatment avenues. ☐

WHY ACUPUNCTURE IS GOING MAINSTREAM

The traditional Chinese technique has been used for millennia to treat chronic pain and other health problems associated with inflammation.

BY ELIZABETH MILLARD

When the opioid addiction crisis began to surge in the U.S. about a decade ago, Medhat Mikhael, MD, spent a lot of time talking to his patients about other ways to heal pain besides opioids, from other types of medications to alternative treatments.

As a pain management specialist at MemorialCare Orange Coast Medical Center in Fountain Valley, California, he didn't anticipate leaving behind the short-term use of opioids altogether, since they work so well for postsurgical pain. But he wanted to recommend a remedy that was safer and still effective. That turned out to be acupuncture.

"Like any treatment, acupuncture doesn't work for everyone, but the majority of my patients who have tried it have found relief," Mikhael says. "When I started looking into studies, I discovered how much evidence there was behind this treatment, and that made me feel comfortable suggesting it as an alternative or a complement to pain medication and other treatments."

That blend of anecdotal success, research-backed results, and a growing level of openness from the medical community are all driving the popularity of acupuncture as a therapy. According to a 2021 World Health Organization (WHO) report, acupuncture is the most widely used traditional medicine practice globally, and it's gaining traction in the U.S. In 2020, the Centers for Medicare & Medicaid Services began covering acupuncture for the first time for chronic low back pain.

Although scientists don't yet understand all the nuances of how acupuncture works, research indicates it can have a significant effect on certain conditions, and it shows promise for others.

What Is Acupuncture?

The goal of acupuncture is the same now as it was thousands of years ago when it was first developed in China: restoring balance to the body, says Kevin Menard, a sports medicine acupuncturist and Traditional Chinese Medicine practitioner in Sag Harbor, New York.

The practice is based on how energy, or *qi,* flows through the body along a series of channels called meridians—similar to the way nerves and vessels carry messages and blood throughout every system.

"According to Chinese medicine theory, each meridian is related to a specific organ, and placing thin needles at certain points along these meridians can effect certain changes in the body to restore homeostasis," Menard explains. The needles aren't the type used to draw blood; they're very thin and flexible, almost like bits of wire.

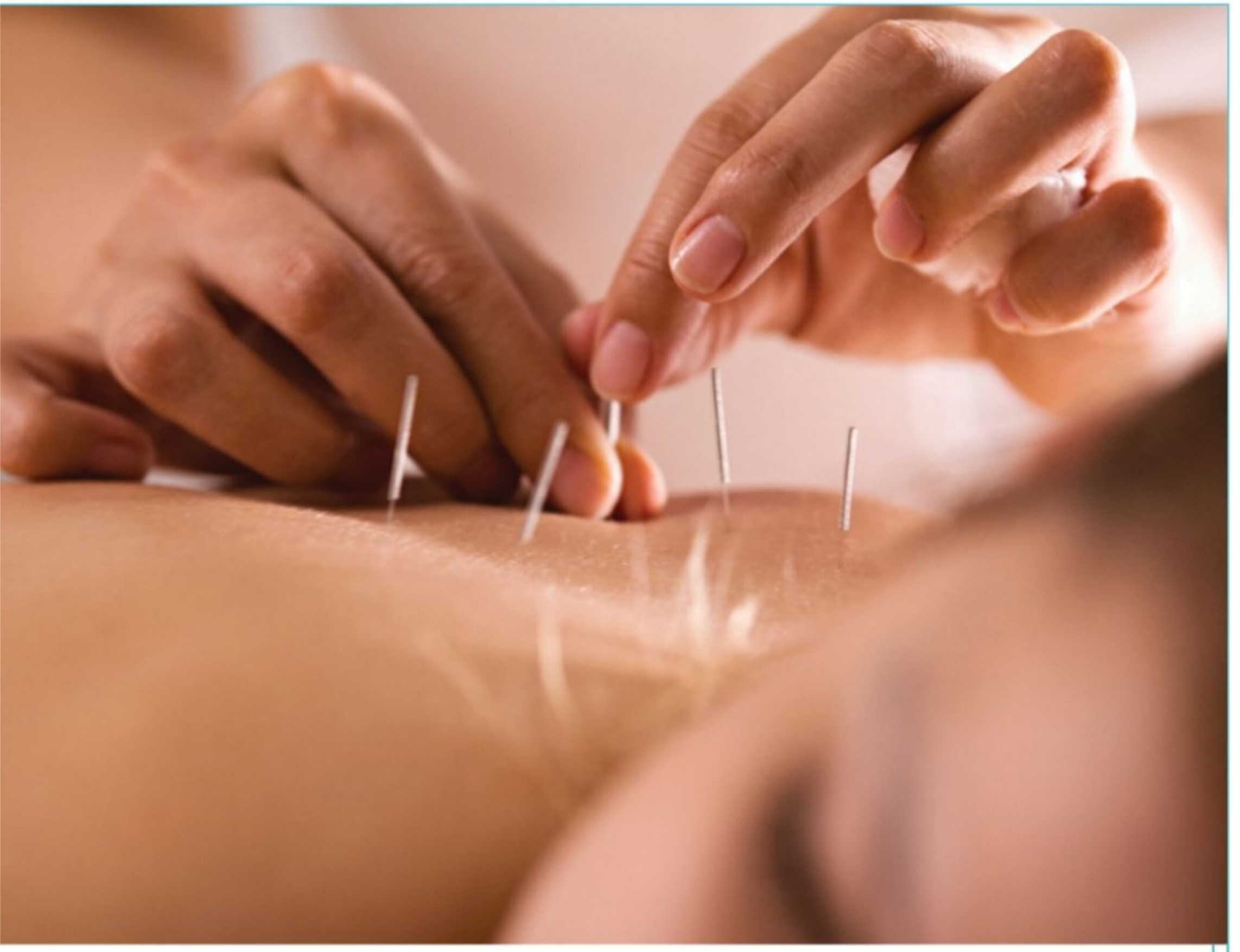
Placement along the meridians is believed to cause reactions such as sending more blood or lymphatic fluid to specific organs or allowing muscles to release in a way that reduces tension on joints and bones. The needles may also stimulate nerves and tweak nervous system regulation to result in a relaxation response, which relieves pain, Mikhael says.

Acupuncture is also thought to stimulate the immune system and control inflammation, says Menard, two effects that can bring benefits throughout the body. Depending on the condition or injury, relief might happen with just one treatment, but it usually takes a series of sessions, Menard says, especially if an issue is complex or chronic.

What the Research Says

Research on acupuncture has been extensive, and so far, robust evidence supports its effectiveness for some, but not all, conditions. According to one analysis published in February 2022 in *BMJ* that analyzed more than 2,000 scientific reviews of acupuncture therapies, the science is strongest behind acupuncture's efficacy for post-stroke aphasia; neck, shoulder, and muscle pain; fibromyalgia pain; lactation issues after delivery; lower back pain; vascular dementia symptoms; and allergy symptoms.

The National Institutes of Health (NIH) has found that acupuncture for pain relief tends to have the most evidence, especially for conditions that have become chronic, such as osteoarthritis and lower back pain, as well as tension headaches. A review of 11 clinical trials also suggests that acupuncture may help with symptoms associated with cancer treatment, the NIH notes.



What's Next in the Field

Acupuncture is far from a proven and accepted therapy for most conditions—even for the ones that show promise. That's in part because the studies that support it are sometimes not of high quality, and the field lacks standardized protocols that would better allow it to be scientifically evaluated, the 2021 WHO report finds.

For instance, one 2016 research review analyzed studies looking at acupuncture for substance abuse and addiction. Among the 83 research articles included in the review, the researchers found substantial variations in study quality, acupuncture frequency, how long needles were left in the body during treatment, which points along the meridians were used, and other potentially important factors. That made it difficult to evaluate how effective the acupuncture really was.

Some potential directions for future studies include studying how acupuncture may affect hormonal regulation, such as alleviating hot flashes in menopause or addressing menstrual irregularity. Research indicates that the practice can boost estrogen and other hormones, and acupuncture for gynecological issues is becoming more popular, says Menard.

Some researchers are also focused on studying acupuncture's impact on fertility. Some small preliminary studies indicate its use may be linked to getting pregnant sooner and having better outcomes from IVF treatments.

Although acupuncture has been used for centuries, only in the past decade has there been a seismic shift in acceptance by both Western medical doctors and patients, Menard says. Ongoing research and increased interest from health systems means that the treatment may be part of more conversations like Mikhael had with his patients.

"At the end of the day, doctors want their patients to feel better, and many people are looking for non-pharmaceutical paths for wellness," Menard says. "Depending on the condition, those little needles can make a huge impact." □

HOW FASTING CAN REPAIR THE GUT

Intermittent fasting may benefit those with a digestive disorder. But does the upside outweigh the risks?

BY MARKHAM HEID

IF YOU SPEND A LOT OF TIME ONLINE, YOU MAY have noticed that parts of the internet have caught fasting fever. Online message boards are awash in posts touting the benefits of time-restricted eating and other intermittent-fasting approaches that involve going without caloric food or drink for an extended period of time—anywhere from 12 hours to several days. These online testimonials have helped popularize intermittent fasting, and they often feature two commonsense rationalizations: one, that human beings evolved in environments where food was scarce and meals occurred sporadically; and two, that the relatively recent shift to near round-the-clock eating has been disastrous for our intestinal and metabolic health.

Mining the internet for accurate information, especially when it comes to dieting, can feel like panning for gold. You've got to sift through a lot of junk to find anything valuable. But this is one case where nuggets may be easy to find. A lot of the published peer-reviewed research on intermittent fasting makes the same claims you'll find on those Reddit message boards. "Until recently, food availability has been unpredictable for humans," wrote the authors of a 2021 review paper in the *American Journal of Physiology*. "Knowledge of early human evolution and data from recent studies of hunter-gatherer societies suggest humans evolved in environments with intermittent periods of food scarcity." They say that fasting regimens may provide a period of "gut rest" that could lead to several meaningful health benefits, including improved gut microbe diversity, gut barrier function, and immune function.

The past decade has witnessed an explosion in fasting-related research. While that work has helped establish links between intermittent fasting and weight loss, as well as other benefits, it's not yet clear when (or if) fasting can help fix a sick gut. "I would still consider the evidence moderate," says Emeran Mayer, MD a professor of medicine and founding director of the Goodman-Luskin Microbiome Center at the University of California, Los Angeles. "[Fast-

ing] looks like a prudent way to maintain metabolic health or reestablish metabolic health, but it's not a miracle cure."

When it comes to gut conditions such as inflammatory bowel disease (IBD), Mayer says the research is either absent or inconclusive. To his point, researchers have found that Ramadan fasting—a monthlong religious period when people don't eat or drink between sunrise and sunset—can substantially "remodel" the gut's bacteria communities in helpful and healthy ways. However, among people with IBD, studies on Ramadan fasting have found that a person's gut symptoms may grow worse.

While it's too early to tout fasting plans as a panacea for gut-related disorders, experts say there's still reason to hope these approaches may emerge as a form of treatment. It's clear that some radical and perhaps radically beneficial things happen when you give your body breaks from food.

Resetting the Gut

For a series of recent studies, a team of researchers based in the Netherlands and China examined the effects of Ramadan-style intermittent fasting on the gut microbiome, the billions of bacteria that reside in the human gastrointestinal tract. (Ramadan comes up a lot in published research because it provides a real-world opportunity for experts to examine the effects of 12- or 16-hour fasts, which is what many popular intermittent fasting diets espouse.) "We really wanted to know what intermittent fasting does to the body," says Maikel Peppelenbosch, PhD, a member of that research team and a professor of gastroenterology at Erasmus University Medical Center in the Netherlands. "Generally, we've seen that intermittent fasting changes the microbiome very clearly, and we view some of the changes as beneficial. If you look at fasting in general, not only Ramadan, you see certain types of bacteria increasing."

For example, Peppelenbosch says that intermittent fasting pumps up the gut's population of a family of bacteria called Lachnospiraceae. "In the intestines, bacteria are constantly battling for ecological space," he explains. Unlike some other gut microorganisms, Lachnospiraceae can survive happily in an empty GI tract: "They can live off the slime the gut makes itself, so they can outcompete other bacteria in a fasting state." Lachnospiraceae produces a short-chain fatty acid called butyrate, which seems to be critically important for gut health. Butyrate sends anti-inflammatory signals to the immune system, which could help reduce pain and other symptoms of gut dysfunction. Butyrate also improves the barrier function of the intestines, Peppelenbosch says. This is, potentially, a very big deal. Poor barrier function (sometimes referred to as "leaky gut") is a hallmark of common GI conditions, including inflammatory bowel disease. If intermittent fasting can turn down inflammation and also help normalize the walls of the GI tract, those changes may have major therapeutic implications.

INTERMITTENT FASTING MAY IMPROVE THE QUALITY OF YOUR SLEEP BY REINFORCING CIRCADIAN RHYTHMS.

Healthy microbiome shifts aren't the only possible benefits that researchers have linked to intermittent fasting. Mayer mentions a phenomenon called the migrating motor complex. "This is rarely mentioned in fasting articles today, but when I was a junior faculty, it was one of the hottest discoveries in gastroenterology research," he says. The migrating motor complex refers to recurrent cycles of powerful contractions that sweep the contents of the gut, including its bacteria, down into the colon. "It's this 90-minute recurring contractile wave that swoops down the intestine, and its strength is comparable to a nutcracker," Mayer explains. Essentially, this motor complex behaves like a street-cleaning crew after a parade. It ensures the gut is cleared out and cleaned up between meals via 90-minute repeating cycles that fasting allows to be become more frequent. It also helps rebalance the gut's microbial populations so that more of them are residing in the colon and lower regions of the GI tract. "But it's stopped the minute you take a bite—it turns off immediately," Mayer says.

He adds that modern eating habits like "grazing," or eating steadily throughout the day, leave little time for the migrating motor complex to do its thing. "This function has been relegated to the time when

we sleep, but even this has been disrupted because a lot of people wake up in the middle of the night and snack on something," Mayer says. "So those longer periods of time when we recleanse and rebalance our gut so that we have normal distributions of bacteria and normal population densities—that has been severely disturbed by these lifestyle changes."

Ideally, Mayer says, people could try to adhere to the kind of time-restricted eating program that allows a full 12 to 14 hours each day for the motor complex to work. "If you don't snack, this motor complex would happen between meals, and you'd also get this 12- to 14-hour window at night where the digestive system was empty," he explains. In other words, sticking to three meals a day and avoiding between-meal bites and nighttime snacks could be sufficient. But again, it's not clear whether this sort of eating schedule can undo gut damage or treat existing dysfunction.

More Potential Benefits

Another possible perk of fasting involves a biological process called autophagy. During autophagy, old or damaged cells die and are cleared away by the body. Some researchers have called it a helpful housekeeping mechanism, and it occurs naturally when the body goes without energy (calories) for an extended period of time. There's been some expert speculation, based mostly on evidence in lab and animal studies, that autophagy could help strengthen the gut or counteract the types of barrier problems seen in people with IBD. But these improvements have not yet been demonstrated in real-world clinical trials involving people.

Meanwhile, some experts have found that fasting may help recalibrate the gut's metabolic rhythms in helpful ways. "By changing the timing of the diet, this will indeed change activity of the microbiome, and that may have downstream impacts on health," says Eran Elinav, MD, PhD, principal investigator of the Host-Microbiome Interaction Research Group at the Weizmann Institute of Science in Israel.

While plenty of unknowns remain, experts say that common approaches to fasting appear to be safe for most people. Time-restricted eating, for example, involves cramming all your day's calories into a single six- to eight-hour eating window. Even among people with metabolic diseases such as type 2 diabetes, research suggests that this form of fasting is safe, provided a person is not taking blood-glucose medications. "We really need much better studies to compare all the different fasting protocols," says Peppelenbosch. "But generally speaking, increasing the space between calorie consumption is a good thing for you. The body is not made to be eating all day." □

LIFT YOUR WAY FIT

Resistance training, such as lifting weights, is a potent exercise that can reduce bone loss and help tame inflammation.

BY MARKHAM HEID

For many, weight training calls to mind bodybuilders pumping iron in pursuit of beefy biceps and bulging pecs. But experts say it's well past time to discard those antiquated notions of what resistance training can do for your physique and health. Modern exercise science shows that working with weights—whether that means light dumbbells or your own body weight—may be the best exercise for lifelong physical function and fitness.

"To me, resistance training is the most important form of training for overall health and wellness," says Brad Schoenfeld, PhD, a professor of exercise science at New York City's Lehman College. During the past decade, Schoenfeld has published more than 30 academic papers on every aspect of resistance training—from the biomechanics of the push-up to the body's nutrient needs following a hard lifting session. Many people think of weight training as exercise that augments muscle size and strength, which is certainly true. But Schoenfeld says the "load" that this form of training puts on bones and their supporting muscles, tendons, and ligaments is probably a bigger deal when it comes to health and physical function.

"We talk about bone resorption, which is a decrease in bone tissue over time," he says. When you're young, bone resorption is balanced and in some cases exceeded by new bone-tissue generation. But later in life, bone tissue losses accelerate and outpace the creation of new bone. That acceleration is especially pronounced among people who are sedentary and women who have reached or passed menopause, Schoenfeld says. This loss of bone tissue leads to the weakness and postural problems that plague many older adults.

"Resistance training counteracts all those bone losses and postural deficits," he explains. Through a process known as bone remodeling, strength training stimulates the development of bone osteoblasts: cells that build bones back up. While you can achieve some of these bone benefits through aerobic exercise, especially in your lower body, resistance training is really the best way to maintain and enhance total-body bone strength.

More research links resistance training with improved insulin sensitivity among people with diabetes and prediabetes. One study published in *Diabetes Care* found that twice-weekly training sessions helped control insulin swings (and body weight) among older men with type 2 diabetes. "Muscle is very metabolically active, and it uses glucose, or blood sugar, for energy," says Mark Peterson, PhD, an associate professor of physical medicine at the University of Michigan.

During a bout of resistance training, your muscles are rapidly using glucose, and this energy consumption continues even after you've finished exercising,

Peterson says. For anyone at risk for metabolic conditions—type 2 diabetes, high blood pressure, unhealthy cholesterol levels, and other symptoms of metabolic syndrome—strength training is among the most effective remedies.

Strength training also seems to be a potent antidote to inflammation, a major risk factor for heart disease and other conditions, says Schoenfeld. A 2010 study out of the University of Connecticut linked regular resistance training with inflammation-quelling shifts in the body's levels of cytokines, a type of immune system protein. Another study from Mayo Clinic found that when overweight women did twice-weekly resistance training sessions, they had a significant drop in several markers of inflammation.

More research has linked strength training to improved focus and cognitive function, better balance, less anxiety, and greater overall well-being.

Some of the latest and most surprising research is in the realm of light-load training, or lifting very small weights. "It used to be thought that you needed to lift heavy loads in order to build muscle and achieve a lot of these benefits," Schoenfeld says. "That's what I was taught in grad school and undergrad. But now it looks like that's completely untrue."

He says lifting "almost to failure"—until your muscles are near the point of giving out—is the real key, regardless of how much weight you're using. "This is a huge boon to adherence, because many older adults or those with injuries or joint issues may not be able to lift heavy loads," he says.

If all that isn't convincing enough to turn you on to weights, perhaps this is: Maintaining strength later in life "seems to be one of the best predictors of survival," says Peterson. "When we add strength… almost every health outcome improves."

"It used to be that we thought of strength training as something for athletes," he adds. "But these days we recognize it as a seminal part of general health and well-being for everyone, at all ages." ☐

The Mind-Body Connection

According to research, yoga and meditation can change the genes that promote inflammation.

BY AMANDA MACMILLAN

Yoga and meditation may do more than just help you feel relaxed in the moment. A new scientific review suggests that these and other mindfulness exercises can actually reverse stress-related changes in genes linked to poor health and depression.

In the paper, published in *Frontiers in Immunology,* British researchers analyzed the findings from 18 previously published studies—involving a total of 846 people—on the biological effects of meditation, yoga, breathing exercises, qigong, and tai chi. Together, the authors say, the studies show that these mind-body exercises appear to suppress the expression of genes and genetic pathways that promote inflammation.

Inflammation can temporarily boost the immune system and can be protective against infection and injury, the authors write in their paper. But in today's society, in which stress is primarily psychological, the body's inflammatory response can become chronic and can impair both physical and mental health.

Researchers found that people who practiced these activities regularly had fewer signs of inflammation, including a decrease in their production of inflammatory proteins. This signals "the reversal of the molecular signature of the effects of chronic stress," they wrote, which may translate to a reduced risk of inflammation-related diseases and conditions.

Environment and lifestyle can both affect which genes are turned on and off, and that can have real effects on disease risk, longevity, and even which traits get passed on to future generations. Stressful events, for example, can activate the fight-or-flight response and trigger a chain reaction of stress-related changes in the body, including activating specific genes involved in making proteins that produce inflammation.

Lead author Ivana Buric, PhD, a researcher in the psychology department at the University of Amsterdam, says her team was surprised to see that different types of mind-body techniques had such similar effects at the genetic level. "Sitting meditation is quite different than yoga or tai chi," she said in an email, "yet all of these activities—when practiced regularly—seem to decrease the activity of genes involved in inflammation."

This is a relatively new field of research, Buric adds, and it's likely that similar benefits could be obtained from other lifestyle changes, such as healthy eating and exercise.

Buric says the existing studies suggest that mind-body interventions "cause the brain to steer our DNA processes along a path that improves our well-being." She also emphasizes that inherited genes are not static, and that DNA activity can depend on things people can control.

"By choosing healthy habits every day, we can create a gene activity pattern that is more beneficial for our health," she says. "Even just 15 minutes of practicing mindfulness seems to do the trick." ☐

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Quick Tricks

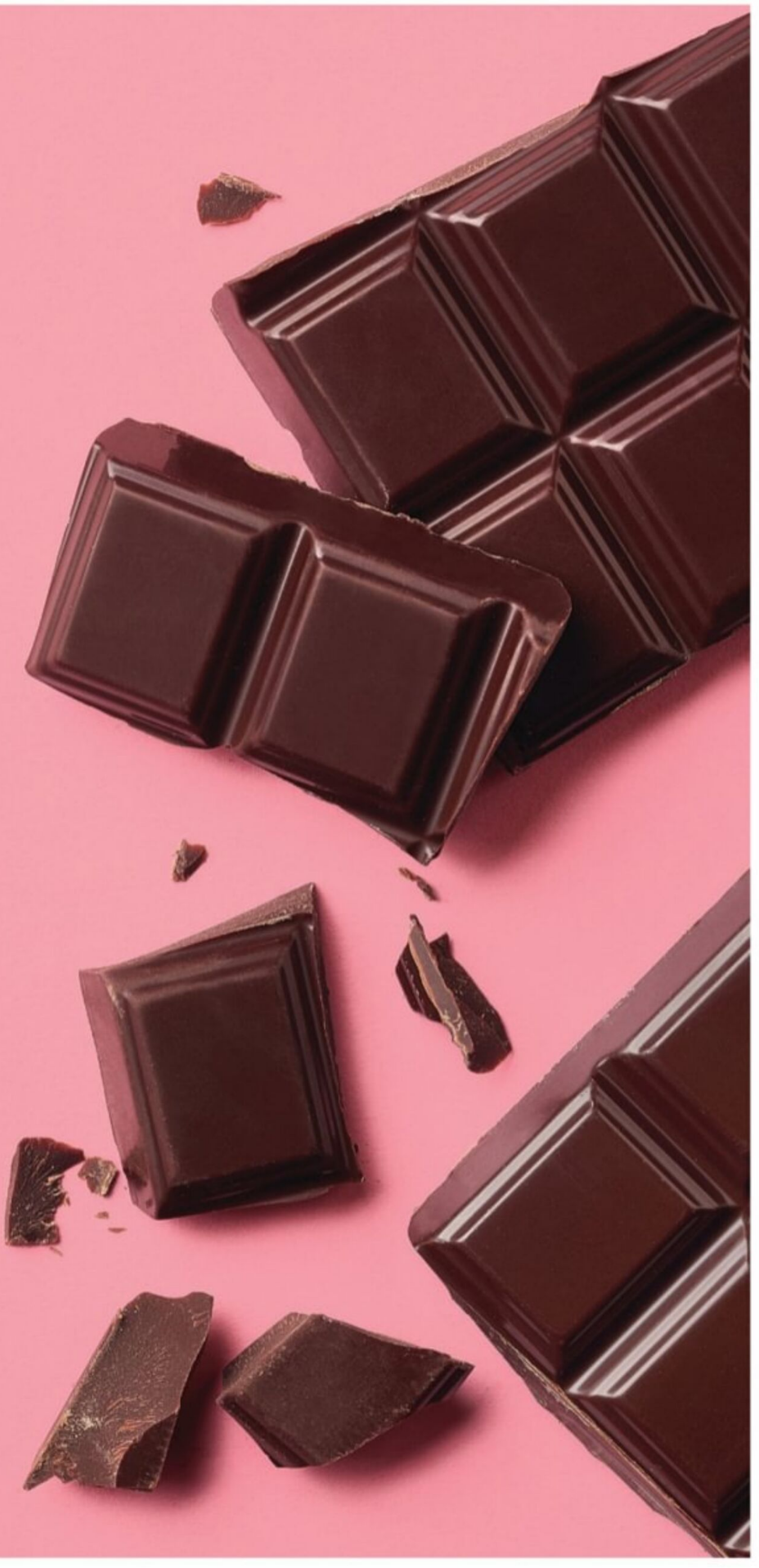
These three tips can jump-start an anti-inflammation plan.

BY AVA ERICKSON

Bite Into Some Dark Chocolate
Dark chocolate with at least 70% cocoa is rich in antioxidants, which have some major anti-inflammatory effects. Flavanols (and dark chocolate is rich in flavonols) can help reduce inflammation and keep the cells that line the arteries healthy. A 2022 study found that cocoa flavanols in particular can improve vascular function and decrease blood pressure and arterial stiffness within three to eight hours after ingestion.

Take a Walk
A 2017 study found that just one 20-minute session of moderate walking significantly reduced the production of cytokine TNF, an inflammatory marker, in immune cells. The study confirmed that even lower-intensity exercise like walking is a powerful way to fight inflammation.

Make Time for Meditation
When the body is stressed, it releases the hormone cortisol. In short spurts, cortisol limits inflammation, but consistently high levels of cortisol can cause inflammation. Meditation, even for just 10 minutes, has been shown to significantly reduce cortisol levels. And studies have directly linked practicing mindful meditation to a decrease in several key inflammatory markers.



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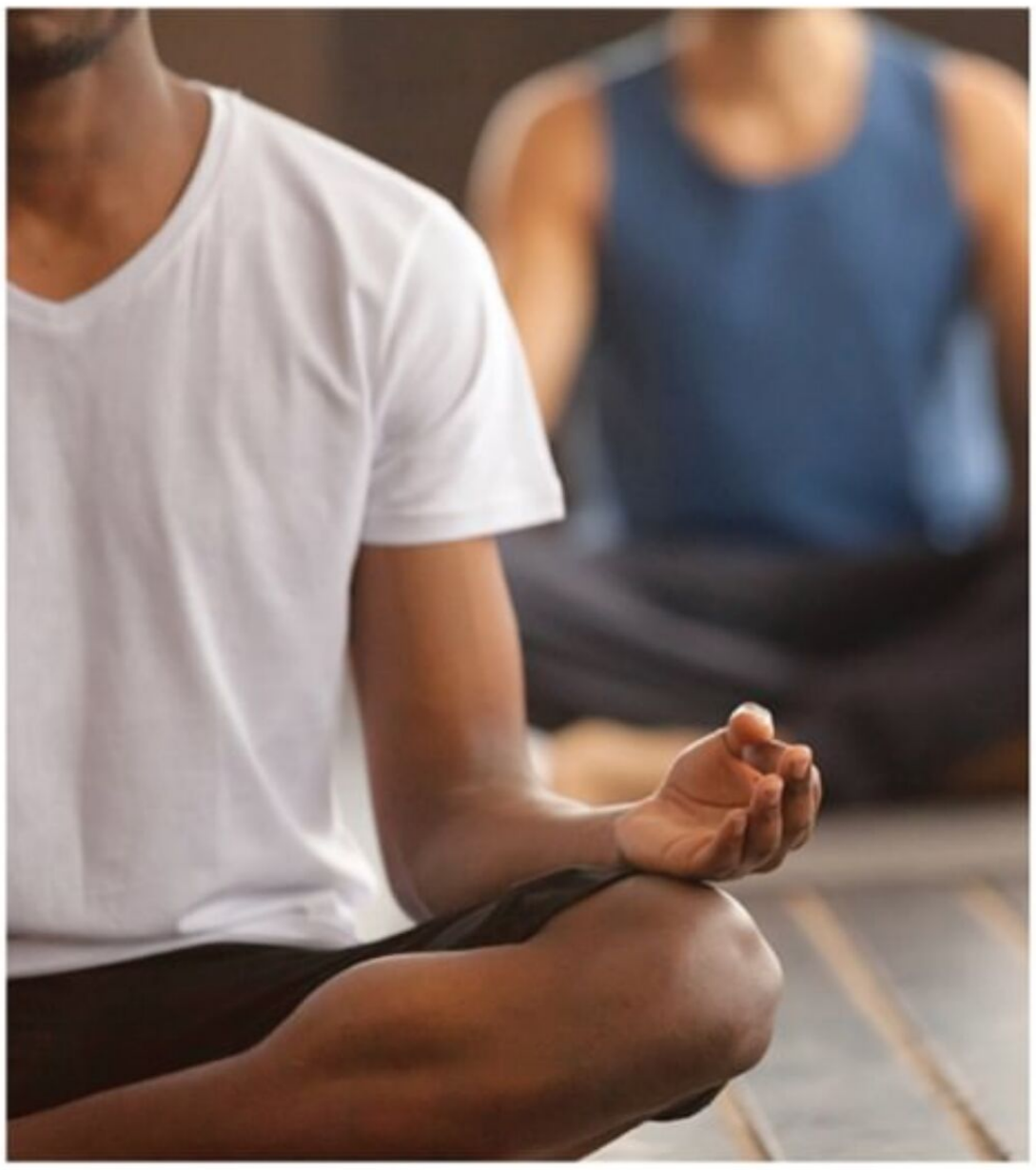
Inflammation is the body's first line of defense against invading infections. But when unchecked, inflammation can harm our systems. Simple shifts in diet and lifestyle can help keep chronic inflammation under control.